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(54) Pharmaceutical compositions comprising labdane diterpenoid derivatives and pyrimido(6,1-a) isoquinolin-4-one derivatives and their use.

(57) Pharmaceutical compositions comprising labdane diterpenoid derivatives and pyrimido(6,1-a)-isoquinolin-4-one derivatives when administered to the skin of a mammal or of the man increase the rate of terminal hair growth, stimulate the conversion of vellus hair to growth as terminal hair and arrest hair loss. They can be used for the treatment of several kinds of alopecia.

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Pharmaceutical compositions comprising labdane diterpenoid derivatives and pyrimido(6,1-a)-isoquinolin-4-one derivatives and their use

The invention described herein relates to pharmaceutical compositions comprising at least one substance selected from the group of compounds named labdane diterpenoid derivatives and at least one substance selected from the group of pyrimido(6,1-a)isoquinoline-4-one derivatives.

Another aspect of the invention is the use of said pharmaceutical compositions for increasing the rate of terminal hair growth, for stimulating the conversion of vellus hair to growth as terminal hair and for arresting the loss of hair as potential methods for the treatment of alopecia.

Alopecia or Baldness is an affliction resulting from loss of hair. Different types of hair loss (alopecia areata, alopecia totalis, androgenetic alopecia) are recognised by dermatologists, the most common by far being known as androgenetic alopecia or male pattern alopecia or baldness. While this type of hair loss is largely confined to males, it is not unknown in women. The condition of alopecia or baldness is a consequence of a combination of factors:

(1) transition of hairs from terminal to vellus,

(2) increased number of telogen hairs - some of which have been shed, and

(3) loss of hair follicles. Very little is known about the cause of male pattern baldness, although it is felt that it could be genetic or hormonal in origin. At the present time, the treatment of male pattern alopecia is attempted either through non-drug related approaches such as hair transplantation, ultra-violet radiation massage, psychiatric treatment and exercise therapy or through drug therapy. The non-drug related approaches to the problem are stated to be either generally ineffective or in the case of transplantation too costly, time-consuming and impractical. In the case of drug therapy, many types of therapeutic drugs ranging from vitamins to hormones, or diphenylhydantoin or streptomycin have been tried and only recently there has been an indication of moderate success. Among treatments which have shown some promise to have grown hair through topical application to the scalp of a human being suffering from male pattern baldness are the use of a microemulsion cream containing estradiol and oxandrolone or organic silicon or minoxidil.

Furthermore, the use of pyrimido(6,1-a)isoquinolin-4-one derivatives for the treatment of alopecia has already been proposed in the German patent application P 38 16 995.9.

Surprisingly, it has now been found that a pharmaceutical composition containing at least one diterpenoid derivative and at least one pyrimido(6,1-a)isoquinolin-4-one derivative is effective for increasing the rate of terminal hair growth, stimulating the conversion of vellus hair to growth as terminal hair and for arresting hair loss. Thus, said pharmaceutical composition is qualified for example for the treatment of alopecia, in particular for the treatment of the male pattern alopecia.

The instant invention relates to a pharmaceutical composition containing at least one compound of group A) consisting of labdane diterpeniods and at least one compound of group B) consisting of pyrimido-(6,1-a(isoquinolin-4-one derivatives.

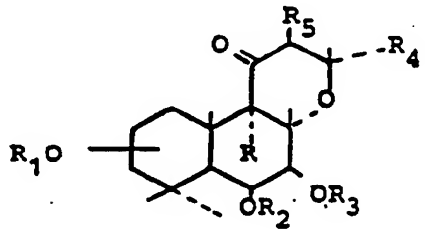
Labdane diterpeniod derivatives, for which a compound named Forskolin isolated from Coleus forskolii (Bhat, Bajura, Dornauer, de Souza, Fehlhaber, Tetrahedron Lett., 1669 (1977), Medicinal Research Reviews, Vol. 3, No. 2, 201 - 219 (1983)) is an example, are described in the following patents and patent applications:

a) Deutsche Offenlegungsschrift 2 557 784
Deutsche Offenlegungsschrift2 654 796
Deutsche Offenlegungsschrift3 502 686
Deutsche Offenlegungsschrift3 502 685
Deutsche Offenlegungsschrift3 535 086
Deutsche Patentanmeldung 37 18 589
Deutsche Patentanmeldung 37 30 748
Indian Patent 147 007
Indian Patent 148 680
Indian Patent Application 345/BOM/84
Indian Patent Application 346/BOM/84
Indian Patent Application 122/BOM/85
Indian Patent Application 50/BOM/87
Indian Patent Application 51/BOM/87
Indian Patent Application 238/BOM/87
Indian Patent Application 265/BOM/87

Indian Patent Application 266/BOM/87

The compounds, in particular the compounds of the examples of said patents patent applications are preferred compounds of group A) of the instant application.

Further preferred compounds of group A) are selected from the compounds characterized by formula I



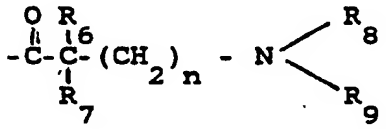
(I)

wherein R denotes H, OH, O-(C_1-C_3)-alkyl or

O

O- C -CH_3 ,

R_1 - R_3 denote independently from each other H, (C_1 -C_6)-alkyl, (C_1-C_6)-alkenyl, (C_1-C_6)-alkynyl, (C_3-C_8)-cycloalkyl, dialkylamino or aralkyl in which the alkyl groups have at most 4 carbon atoms, (C_1-C_{20})-acyl, (C_2-C_{10})-alkoxycarbonyl, (C_2-C_{10})-arylaminocarbonyl or either all three or only two or one of the substituents R_1, R_2 and R_3 denote the radical of formula II



(II)

and the other or others hydrogen, where

R_6 and R_7 are identical or different and represent hydrogen, (C_1-C_6)-alkyl or an aryl radical,

n stands for 0 or an integer from 1 to 10,

R_8 denotes hydrogen if R_9 represents hydrogen, unsubstituted or substituted (C_1-C_6)-alkyl, (C_5-C_7)-cycloalkyl, aryl-(C_1-C_2)-alkyl, aryl, a heterocyclic hydrocarbon wherein the heteroatoms may be oxygen, nitrogen or sulfur, optionally substituted amino, hydroxyl, acyl, di-(C_1-C_6)-alkylamino, carbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyl-(C_1-C_6)-alkyl, or

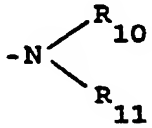
R_8 and R_9 have the same meaning and stand for optionally substituted (C_1-C_6)-alkyl, aryl, or aryl-(C_1-C_2)-alkyl, or

R_8 denotes (C_1-C_6)-alkyl and R_9 represents substituted (C_1-C_6)-alkyl, (C_5-C_7)-cycloalkyl, aryl-(C_1-C_6)-alkyl or di-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl, or

R_8 and R_9 together with the N-atom to which they are attached represent a heterocyclic hydrocarbon which in addition to the N-atom may contain one or more heteroatoms from the group comprising nitrogen, oxygen and sulfur and may be singly or multiply substituted by (C_1-C_6)-alkyl, aryl-(C_1-C_6)-alkyl, hydroxy-(C_1-C_6)-alkyl, aryl, hydroxyl or further heterocyclic hydrocarbons, or

R_1, R_2 and/or R_3 denote - $\overset{Z}{\overset{\|}{C}}$ -A, in which Z represents oxygen or sulfur,

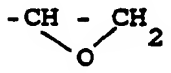
and A either represents the radical



in which R_{10} represents hydrogen or (C_1-C_6)-alkyl, and

R_{11} represents (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, aryl, aryl-(C_1-C_6)-alkyl, (C_2-C_6)-carbalkoxy or sulfonylaryl,

or
R_{10} and R_{11}, together with the nitrogen atom to which they are bonded, form a heterocycle which may contain as further heteroatom oxygen, nitrogen or sulfur, or A represents the radical $-OR_{12}$ in which
R_{12} represents (C_1-C_6)-alkyl or halogeno-(C_1-C_6)-alkyl, or
R_1 represents a tris-(C_1-C_6)-alkyl-silyl group, and
R_2 and R_3 have the meanings given above,
R_4 denotes ethyl, a vinyl group,-CHO,



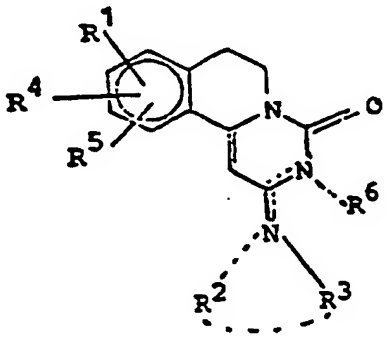
or
$-CH(OX)CH_2OX$, where X is H or $-C(O)-(C_1-C_3)$-alkyl and
R_5 denotes H, OH or $O-(C_1-C_3)$-alkyl and the pharmaceutically accpetable salts thereof.

Particularly preferred pharmaceutical compositions are those, wherein the compounds of group A) are selected from the group of compounds of formula I as described above, which are characterized by at least one of the following attributes:
R denotes H or OH,

R_1 - R_3 denote independently from each other H or
O
||
- C -(C_1-C_3)-alkyl or either all three, two or one of the substituents R_1 - R_3 denote the group of formula II, as described above, in which n is an integer from 0 to 5, and the other(s) denote H,
R_6 and R_7 represent H or R_6 represents hydrogen and R_7 represents (C_1-C_4)-alkyl,
R_8 represents (C_1-C_{10})-alkyl and
R_9 represents cyclohexyl or R_8 and R_9 together with the N-atom to which they are attached represent the piperidino, morpholino, thiomorpholino, piperazino, imidazole, theophyllino or pyrrolidino radical,
R_4 denotes vinyl or $CHOHCH_2$ OH and
R_5 denotes H.

Many from the compounds of group A) may form salts from organic or inorganic acids. Suitable examples of salts from organic or inorganic acids are hydrochloride, hydrobromide, sulfate, phosphate, acetate, oxalate, tartrate, citrate, maleate or fumarate.

The compounds of group B) for which Trequinsin (cf. IRCS Med. Sci. 1981, 9, 325; Life Sci., 1984, 31, 2037; Naunyn-Schmiedeberg's Arch. Pharmacol., 1982, 319, Suppl. R49) is an example, are explicitly described in b) Deutsche Offenlegungsschriften 27 20 085 and 28 01 289 and in the Indian patents 147 624, 149 432 and 149 457. Preferred compounds are described and exemplified in the patent applications cited under b). Further preferred compounds of group B) are characterized by the formula III

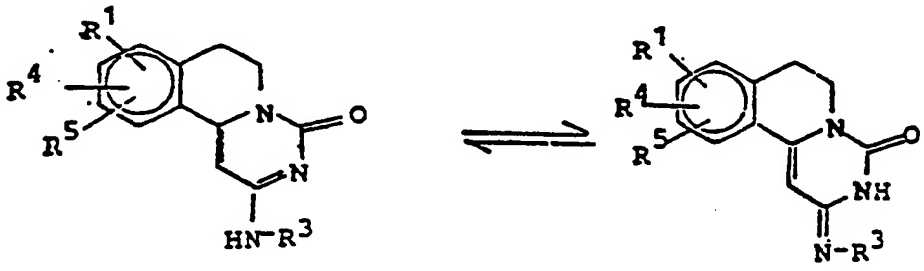


III

in which
R^1, R^4 and R^5, which may be the same or different, stand for hydrogen, hydroxy, lower alkoxy, dialkylphosphinylalkoxy, acyloxy or halogen,
two of the radicals R^1, R^4 or R^5, when in adjacent positions and taken together, may form a methylenedioxy or ethylenedioxy group,

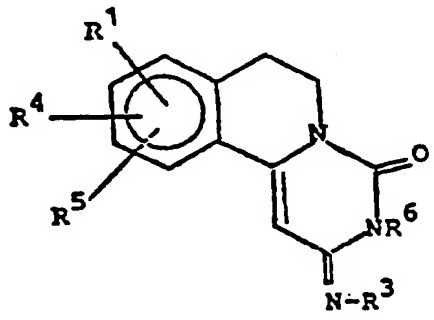
R^2 and R^3, which may be the same or different, stand for hydrogen; hydroxy, lower alkoxy, amino, alkylamino, dialkylamino, arylamino, amino or alkyl substituted by a 5-or 6-membered carbon ring containing up to 3 hetero atoms selected from the group of N, O and S; alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, acyl and optionally substituted aryl, aryl denoting an aromatic hydrocarbon radical having up to 10 carbon atoms;
R^2 represents a pair of electrons if R^6 stands for one of the radicals defined below and
R^2 and R^3 when taken together with the nitrogen atom to which they are bound may form an optionally substituted nitrogen heterocycle possibly containing a further nitrogen or oxygen atom, and
R^6 stands for hydrogen, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, heterocyclically substituted alkyl, dialkyl-phosphinylalkyl, acyl and optionally substituted aryl or
R^6 represents a pair of electrones if R^2 represents one of the radicals defined above;
and the acid addition salts and quaternary ammonium salts thereof.

In the case of at least one of the two radicals R^2 and R^3 being hydrogen, the above definition of the pyrimido(6,1-a)isoquinolin-4-one derivatives also encompass the isomers of the following formula Ib, obtained by complete isomerization of compounds of formula Ia or being in equilibrium with the compounds of formula Ia.



Ia Ib

The definition of the pyrimido(6,1-a)isoquinolin-4-one derivatives also encompass the isomer of formula Ic



Ic

in which R^1, R^3, R^4, R^5 and R^6 have the above meanings. If R^1, R^2, R^3, R^4 and R^5 stand for lower alkoxy groups, those having up to 3 carbon atoms are suitable.

Suitable acyloxy radicals for R^1, R^4 or R^5 are those in which the acyl group is linear or branched (C_1-C_6)-alkanoyl, for example acetyl, or aroyl, especially benzoyl in which the phenyl nucleus may be substituted one to three times by halogen, nitro, hydroxy, (C_1-C_3)-alkoxy and (C_1-C_3)-alkyl. If R^1, R^4 or R^5

stand for halogen, chlorine is preferred. Suitable dialkylphosphinylalkoxy radicals for R^1, R^4 or R^5 are those in which the alkyl and alkoxy groups carry at most 3 carbon atoms, for example dimethylphosphinylmethoxy.

Especially suitable alkylamino or dialkylamino radicals for R^2 or R^3 are those in which the alkyl groups have at most 3 carbon atoms, for example methylamino or dimethylamino.

Suitable arylamino radicals for R^2 or R^3 are phenylamino radicals in which the phenyl residue may be substituted one or several times by halogen, for example chlorine, (C_1-C_3)-alkyl, for example methyl, or nitro. A suitable nitrogen-containing heterocyclic amino radical for R^2 or R^3 is, for example, the N-morpholinoamino radical.

As alkyl radical for R^2, R^3 or R^6 there can be used those having at most 6 carbon atoms, for example methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec.butyl or tert.butyl.

Suitable cycloalkyl radicals for R^2, R^3 and R^6 are those having at most 6 carbon atoms, for example cyclohexyl.

In the case of R^2, R^3 or R^6 being a substituted alkyl radical there may be used those having up to 6 carbon atoms and substituted by one or two hydroxy or (C_1-C_3)-alkoxy groups, halogen atoms, for example chlorine, amino or di-(C_1-C_4)-alkyl-amino, dialkylphosphinylalkyl, for example dimethylphosphinylmethyl.

Examples of aralkyl radical for R^2, R^3 and R^6 are those having at most 8 carbon atoms, in which the aryl radical may be mono- or polysubstituted, especially substituted one, two, or three times by the substituents defined above for R^1.

Suitable heterocyclic alkyl radicals for R^2, R^3 and R^6 are, for example, furfuryl and tetrahydrofurfuryl.

Suitable examples of aryl radicals for R^2, R^3 and R^5 are phenyl radicals optionally substituted one or several times, preferably one, two or three times by halogen, for example fluorine, chlorine and bromine, (C_1-C_3)-alkyl and (C_1-C_3)-alkoxy, for example methyl, ethyl, methoxy and ethoxy, haloalkyl, for example trifluoromethyl, amino or hydroxy, in the latter the hydrogen atoms possibly being replaced by an alkali metal, for example sodium.

Suitable nitrogen-containing heterocyclic radicals are, for example, pyrrolidino, piperidino, morpholino, and piperazino, optionally substituted by alkyl, alkoxycarbonyl, aryl or a nitrogen heterocycle, the terms alkyl, alkoxy, aryl and nitrogen heterocycle having the above meaning.

Examples of suitable acyl radicals for R^2, R^3 and R^6 are linear or branched (C_1-C_6)-alkanoyl, such as acetyl, or aroyl, such as benzoyl, wherein the phenyl residue may be substituted one or several times by the substituents defined above for R^2, R^3 and R^6 when they represent an aryl radical.

As salts of the pyrimido(6,1-a)isoquinolin-4-one derivatives of the invention there are mentioned by way of example those of inorganic or organic acids, for example the hydrochlorides, hydrobromides, sulfates, phosphates, acetates, oxalates, tartrates, citrates, maleates or fumarates.

Suitable quaternary ammonium salts of the pyrimido(6,1-a)-isoquinolin-4-one derivatives of the invention are, for example, the salts derived from alkyl halides, such as methiodides.

Preferred substituents are:

alkoxy for R^1 and R^4, hydrogen for R^5, (C_1-C_6)-alkyl or phenyl optionally substituted one to three times as defined above for R^2, hydrogen, (C_1-C_6)-alkyl, cycloalkyl, substituted alkyl, aralkyl, heterocyclic alkyl, substituted aryl and (C_1-C_6)-alkanoyl for R^3 and R^6.

Particularly preferred compounds are:

9,10-dimethoxy-2-tert.-butylamino-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoline-4-one hydrochloride,

9,10-dimethoxy-2-(2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)-isoquinolin-4-one hydrochloride dihydrate,

9,10-dimethoxy-3-methyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-2-(N-methyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-3-isopropyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-2-(N-isopropyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-3-ethyl-2-mesitylimino-2,3,6,7-tetrahydro4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-2-(N-ethyl-2,4,6.trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-3-acetyl-2-mesitylimino-2,3,6,7-tetrahydro4H-pyrimido(6<1-a)isoquinolin-4-one and

9,10-dimethoxy-2-(N-acetyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one.

The production of the compounds of groups A) and B) is explicitly described in the patents and patent

applications cited above under a) and b).

A pharmaceutical composition with extraordinary activity contains 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one and 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido-(6,1-a)isoquinolin-4-one hydrochloride.

Detailed investigations have shown that the combined topical administration of at least one compound of group A) and at least one compound of group B) results in an activity on hair growth which is far in excess of that which would result when said compounds are used singly; thus, said combinations show a clear synergistic effect. An important advantage of the pharmaceutical compositions according to the instant invention is the fact that the compounds of group A) and group B) have an influence on hair growth through different mechanisms.

The pharmaceutical compositions according to the instant invention can be administered to any mammals, however, they have a special importance for the human being.

For the increase of hair growth and for the treatment of alopecia (e.g. alopecia areata, alopecia totalis or androgenetic alopecia) a combination of one or more compounds of group A) and one or more compounds of group B) is administered, preferably topically, optionally together with suitable carriers and/or excipients. Examples of application forms which may be mentioned are solutions, suspensions, emulsions, pastes, ointments, soaps, jellies, creams, lotions, dusting powders, surfactant cotaing cleansing products, oils, sprays, aerosols and the like.

Any desired carriers and/or excipients are added to the pharmaceutical composition. Excipients which are to be preferred are derived from the group of preservatives, antioxidants, stabilizers, solubilizers, vitamins, colorants and odor improvers.

Ointments, pastes, creams and jellies can, besides the active substance(s), contain the customary excipients, for example animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonite, silica, talc and zinc oxide, or mixtures of these substances.

Dusting powders and sprays can, besides the active substance(s), contain the customary excipients, for example lactose, talc silica, aluminum hydroxide, calcium silicate and polyamide powder, or mixtures of these substances. Sprays can additionally contain the customary propellants, for example chlorofluorohydrocarbons, propane/butane or dimethyl ether.

Solutions and emulsions can, besides the active substance(s), contain the customary excipients such as solvents, solubilizers and emulsifiers, for example water, ethanol, isopropanol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylen glycol, dimethylacetamide, 1,3-butylglycol, oils, especially cottonseed oil, peanut oil, corn oil, olive oil, castor oil and sesame oil, glycerol fatty acid esters, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances.

Suspensions can, besides the active substance(s), contain the customary excipients such as liquid diluents, for example water, ethanol or propylene glycol, suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances.

Soaps can, besides the active substance(s), contain the customary excipients such as, for example, alkali metal salts or fatty acids, salts of fatty acid hemiesters, fatty acid protein hydrolyzates, isethionates, lanolin, fatty alcohols, vegetable oils, plant extracts, glycerol, sugar, or mixtures of these substances.

Surfactant-containing cleansing products can, besides the active substance(s), contain the customary excipients such as, for example, salts of fatty alcohol sulfates, fatty alcohol ether sulfates, sulfosuccinic hemiesters, fatty acid protein hydrolyzates, isethionates, imidazolinium derivatives, methyllaurates, sarcosinates, fatty acid amide ether sulfates, alkylamidobetaines, fatty alcohols, fatty acid glycerides, fatty acid diethanolamides, vegetable and synthetic oils, lanolin derivatives, ethoxylated glycerol fatty acid esters, or mixtures of these substances.

Oils can, besides the active substance(s), contain the customary excipients such as, for example, synthetic oils such as fatty acid esters, fatty alcohols, silicone oils, neutral oils such as vegetable oils, and oily plant extracts, liquid paraffins, lanolin oil, or mixtures of these substances.

A physiologically effective amount of a pharmacologically acceptable composition is applied to the scalp as often as required. A preferred concentration of the compounds of group A) and the compounds of group B) in combination, when administered as topical solution to the scalp is in the range of 0.1 % to 5 %.

The particularly preferred range of concentration is 0.5 - 3 %. The ratio of the compounds of group A) to the compounds of group B) may vary from 1:99 to 99:1. The preferred solvents for solutions are such as water, ethanol, propylene glycol, dimethylacetamide, used singly or in combination in appropriate proportion to keep the active ingredients in solution. The number of administrations per day to the deltoid areas is dependent on the concentration of the active ingredient(s) administered. Application of the solutions may be made by way of contact occlusion to the deltoid areas. Occlusion of the solution may be obtained by any

conventional means such as bandages, plastic coverings, shower caps, swimming caps etc.

The following examples illustrate the invention but are not to be construed as limiting.

Example 1:

One thousand ml of an aqueous solution containing 2 % 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride and 2 % 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one is prepared from the following types and amount of ingredients.

9,10-Dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride	20 g
7β-Acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one	20 g
Propylene glycol	250 g
Polyethylene glycol	400 g
Ethyl alcohol	300 g
Dionised water q.s. ad	1000 ml

The ingredients 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)-isoquinolin-4-one hydrochloride and 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one are dissolved separately into propylene glycol and polyethylene glycol maintaining the temperature of 35 - 45° C. The solutions are then cooled to room temperature and mixed under stirring and further diluted with ethanol first and then with water to make the volume of the solution to 1000 ml. The resulting solution is sterilised by filtration. The solution is then filled aseptically into sterile containers.

Example 2:

A solution containing 1 % 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride and 1% 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one is prepared from the following amount of ingredients

9,10-Dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride (Trequisin)	1 g
7β-Acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one (Forskolin)	1 g
Propylene glycol	40 ml
Ethyl alcohol q.s.ad	100 ml

The ingredients 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)-isoquinolin-4-one hydrochloride and 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one are dissolved in propylene glycol at room temperature under stirring and further diluted with ethanol to make the volume of the solution to 100 ml. The resulting solution is sterilised by filtration. The solution is then filled aseptically into sterile containers.

The solutions were also prepared similarly using tetraglycol in place of a mixture of polyethylene glycol and propylene glycol in the above example.

The solutions so prepared can be used in the topical application for treatment of male pattern baldness by application to the affected area of the scalp daily.

Detection of hair growth-promoting effect of Forskolin + Trequisin.

Male and female rabbits having a weight of 500 - 700 g and an age of 5 - 6 weeks were used for the

experiments. The animals were kept with the mother during the entire experiment.

The rear part of the experimental animals was shaved in four sites (two on each side) using electric hair clippers. Each animal had 4 shaved sites of 3 cm^2 each. 18 hours after shaving, 0.2 ml of test solution (see Example 2) and also solvent as a blank sample were placed on each shaved site and massaged in for about 60 sec. The application was repeated daily and at the end of each week in each case 10 hairs were pulled out from each site and their length was determined.

Solution of a mixture of Trequisin and Forskolin having a content of 1 % of each active compound was used.

Results obtained are shown in Table 1.

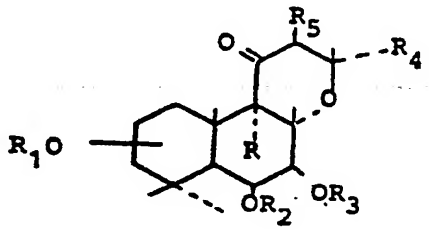
Table 1

Hair growth in mm in rabbits under the influence of treatment with a solution containing Trequisin and Forskolin		
Treatment period in weeks	Solvent	Solution containing Trequisin + Forskolin
1	9.88 ± 0.38	10.32 ± 0.49
4	13.78 ± 0.91	15.38 ± 0.91
5	19.10 ± 0.88	22.26 ± 0.89

Claims

1. A pharmaceutical composition containing at least one compound of group A) consisting of labdane diterpenoid derivatives and at least one compound of group B) consisting of pyrimido(6,1-a)isoquinolin-4-one derivatives.

2. A pharmaceutical composition as claimed in claim 1, wherein the compounds of group A) are selected from the compounds characterized by the formula I

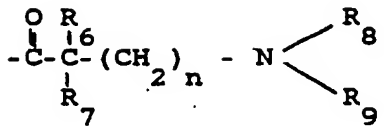


(I)

wherein R denotes H, OH, O-(C_1-C_3)-alkyl or

O-C(=O)-CH_3 ,

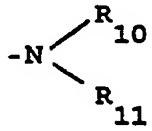
R_1 - R_3 denote independently from each other H, (C_1-C_6)-alkyl, (C_1-C_6)-alkenyl, (C_1-C_6)-alkynyl, (C_3-C_8)-cycloalkyl, dialkylamino or aralkyl in which the alkyl groups have at most 4 carbon atoms, (C_1-C_{20})-acyl, (C_2-C_{10})-alkoxycarbonyl, (C_2-C_{10})-arylaminocarbonyl or either all three or only two or one of the substituents R_1, R_2 and R_3 denote the radical of formula II



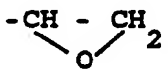
(II)

and the other or others hydrogen, where R_6 and R_7 are identical or different and represent hydrogen, (C_1-C_6)-alkyl or an aryl radical, n stands for 0 or an integer from 1 to 10, R_8 denotes hydrogen if R_9 represents hydrogen, unsubstituted or substituted (C_1-C_6)-alkyl, (C_5-C_7)-cycloalkyl, aryl-(C_1-C_2)-alkyl, aryl, a heterocyclic hydrocarbon wherein the heteroatoms may be oxygen, nitrogen or sulfur, optionally substituted amino, hydroxyl, acyl, di-(C_1-C_6)alkylamino, carbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)alkylcarbonyl-(C_1-C_6)-alkyl, or R_8 and R_9 have the same meaning and stand for optionally substituted (C_1-C_6)-alkyl, aryl, or aryl-(C_1-C_2)-alkyl, or R_8 denotes (C_1-C_6)-alkyl and R_9 represents substituted (C_1-C_6)-alkyl, (C_5-C_7)-cycloalkyl, aryl-(C_1-C_6)-alkyl or di-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl, or R_8 and R_9 together with the N-atom to which they are attached represent a heterocyclic hydrocarbon which in addition to the N-atom may contain one or more heteroatoms from the group comprising nitrogen, oxygen and sulfur and may be singly or multiply substituted by (C_1-C_6)-alkyl, aryl-(C_1-C_6)-alkyl, hydroxy-(C_1-C_6)-alkyl, aryl, hydroxyl or further heterocaclic hydrocarbons, or

R_1, R_2 and/or R_3 denote - C(=Z) -A, in which Z represents oxygen or sulfur,
and A either represents the radical



in which R_{10} represents hydrogen or (C_1-C_6)-alkyl, and R_{11} represents (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, aryl, aryl-(C_1-C_6)-alkyl, (C_2-C_6)-carbalkoxy or sulfonylaryl, or R_{10} and R_{11}, together with the nitrogen atom to which they are bonded, form a heterocycle which may contain as further heteroatom oxygen, nitrogen or sulfur, or A represents the radical $-OR_{12}$ in which R_{12} represents (C_1-C_6)-alkyl or halogeno-(C_1-C_6)-alkyl, or R_1 represents a tris-(C_1-C_6)-alkyl-silyl group, and R_2 and R_3 have the meanings given above, R_4 denotes ethyl, a vinyl group, -CHO,

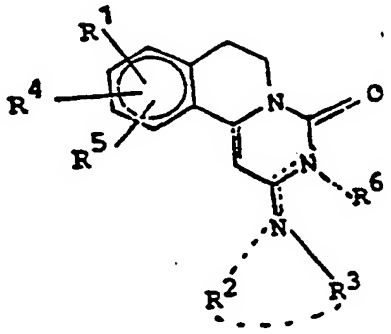


or
$-CH(OX)CH_2OX$, where X is H or -C(O)-(C_1-C_3)-alkyl and R_5 denotes H, OH or O-(C_1-C_3)-alkyl and the pharmaceutically acceptable salts thereof.

3. A pharmaceutical composition as claimed in claim 1, wherein the compounds of group A) are selected from the group of compounds of formula I as claimed in claim 2, which are characterized by at least one of the following attributes:
R denotes H or OH,
R_1 - R_3 denote independently from each other H or
O
- C -(C_1-C_3)-alkyl or all three, two or one of the substituents R_1 - R_3 denote the group of formula II, as described above, in which n is an integer from 0 to 5 and the other(s) denote H,
R_6 and R_7 represent H or R_6 represents hydrogen and R_7 represents (C_1-C_4)-alkyl,
R_8 represents (C_1-C_{10})-alkyl and
R_9 represents cyclohexyl or R_8 and R_9 together with the N-atom to which they are attached represent the piperidino, morpholino, thiomorpholino, piperazino, imidazole, theophyllino or pyrrolidino radical,
R_4 denotes vinyl or $CHOHCH_2OH$ and
R_5 denotes H.

4. A pharmaceutical composition as claimed in claim 1, wherein the compounds of group B) are

selected from the compounds characterized by the formula III



(III)

in which
R^1, R^4 and R^5, which may be the same or different, stand for hydrogen, hydroxy, lower alkoxy, dialkylphosphinylalkoxy, acyloxy or halogen, two of the radicals R^1, R^4 or R^5, when in adjacent positions and taken together, may form a methylenedioxy or ethylenedioxy group,
R^2 and R^3, which may be the same or different, stand for hydrogen, hydroxy, lower alkoxy, amino, alkylamino, dialkylamino, arylamino, amino or alkyl substituted by a 5- or 6-membered carbon ring containing up to 3 hetero atoms selected from the group of N, O and S; alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, acyl and optionally substituted aryl, aryl denoting an aromatic hydrocarbon radical having up to 10 carbon atoms;
R^2 represents a pair of electrons if R^6 stands for one of the radicals defined below and
R^2 and R^3 when taken together with the nitrogen atom to which they are bound may form an optionally substituted nitrogen heterocycle possibly containing a further nitrogen or oxygen atom, and
R^6 stands for hydrogen, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, heterocyclically substituted alkyl, dialkylphosphinylalkyl, acyl and optionally substituted aryl or
R^6 represents a pair of electrones if R^2 represents one of the radicals defined above;
and the acid addition salts and quaternary ammonium salts thereof.

5. A pharmaceutical composition as claimed in claim 1, wherein the compounds of group B) are selected from the following compounds:
9,10-dimethoxy-2-tert.-butylamino-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoline-4-one hydrochloride,
9,10-dimethoxy-2-(2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride dihydrate,
9,10-dimethoxy-3-methyl-2-mesitylimino-2,3,6,7-tetrahydro4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-2-(N-methyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-3-isopropyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-2-(N-isopropyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-3-ethyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-2-(n-ethyl.2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-3-acetyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one or
9,10-dimethoxy-2-(N-acetyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one.

6. A pharmaceutical composition as claimed in claim 1 containing
7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one and 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride.

7. The use of a pharmaceutical composition as claimed in one or more of claims 1 - 6 for hair growth and for arrest of hair loss.

8. The use of a pharmaceutical composition as claimed in one or more of claims 1 - 6 for the treatment of androgenetic alopecia, alopecia areata and alopecia totalis.

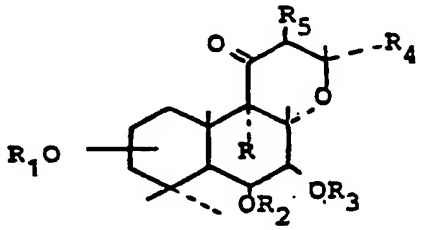
9. Pharmaceutical composition as claimed in one or more of claims 1 - 6 for topical administration.

10. Process for the production of a pharmaceutical composition as claimed in claims 1 - 6 or 9, wherein at least one compound of group A) and at least one compound of group B) are, together with acceptable carriers and/or excipients, transformed into a form suitable for administration.

Claims for the following Contracting States: ES, GR

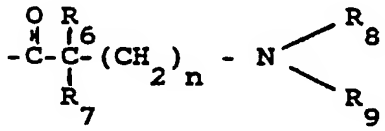
1. A process for the preparation of a pharmaceutical composition wherein at least one compound of group A) consisting of labdane diterpenoid derivatives and at least one compound of group B) consisting of pyrimido(6,1-a)isoquinolin-4-one derivatives are transformed into a form suitable for administration

2. A process as claimed in claim 1, wherein the compounds of group A) are selected from the compounds characterized by the formula I



(I)

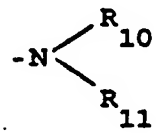
wherein R denotes H, OH, O-(C_1-C_3)-alkyl or O-$\overset{O}{\overset{\|}{C}}$-$CH_3$, R_1 - R_3 denote independently from each other H, (C_1-C_6)-alkyl, (C_1-C_6)-alkenyl, (C_1-C_6)-alkynyl, (C_3-C_8)-cycloalkyl, dialkylamino or aralkyl in which the alkyl groups have at most 4 carbon atoms, (C_1-C_{20})-acyl, (C_2-C_{10})-alkoxycarbonyl, (C_2-C_{10})-arylaminocarbonyl or either all three or only two or one of the substituents R_1, R_2 and R_3 denote the radical of formula II



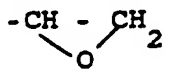
(II)

and the other or others hydrogen, where R_6 and R_7 are identical or different and represent hydrogen, (C_1-C_6)-alkyl or an aryl radical, n stands for 0 or an integer from 1 to 10, R_8 denotes hydrogen if R_9 represents hydrogen, unsubstituted or substituted (C_1-C_6)-alkyl, (C_5-C_7)-cycloalkyl, aryl-(C_1-C_2)-alkyl, aryl, a heterocyclic hydrocarbon wherein the heteroatoms may be oxygen, nitrogen or sulfur, optionally substituted amino, hydroxyl, acyl, di-(C_1-C_6)alkylamino, carbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)alkylcarbonyl-(C_1-C_6)-alkyl, or R_8 and R_9 have the same meaning and stand for optionally substituted (C_1-C_6)-alkyl, aryl, or aryl-(C_1-C_2)-alkyl, or R_8 denotes (C_1-C_6)-alkyl and R_9 represents substituted (C_1-C_6)-alkyl, (C_5-C_7)-cycloalkyl, aryl-(C_1-C_6)-alkyl or di-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl, or R_8 and R_9 together with the N-atom to which they are attached represent a heterocyclic hydrocarbon which in addition to the N-atom may contain one or more heteroatoms from the group comprising nitrogen, oxygen and sulfur and may be singly or multiply substituted by (C_1-C_6)-alkyl, aryl-(C_1-C_6)-alkyl, hydroxy-(C_1-C_6)-alkyl, aryl, hydroxyl or further heterocaclic hydrocarbons, or

R_1, R_2 and/or R_3 denote -$\overset{Z}{\overset{\|}{C}}$-A, in which Z represents oxygen or sulfur, and A either represents the radical



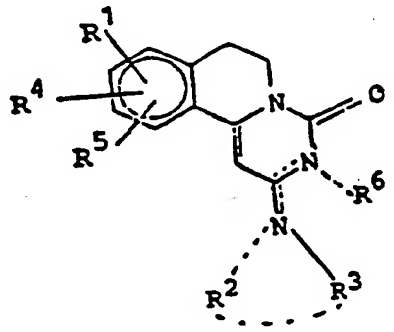
in which R_{10} represents hydrogen or (C_1-C_6)-alkyl, and R_{11} represents (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, aryl, aryl-(C_1-C_6)-alkyl, (C_2-C_6)-carbalkoxy or sulfonylaryl, or R_{10} and R_{11}, together with the nitrogen atom to which they are bonded, form a heterocycle which may contain as further heteroatom oxygen, nitrogen or sulfur, or A represents the radical $-OR_{12}$ in which
R_{12} represents (C_1-C_6)-alkyl or halogeno-(C_1-C_6)-alkyl, or R_1 represents a tris-(C_1-C_6)-alkyl-silyl group, and R_2 and R_3 have the meanings given above, R_4 denotes ethyl, a vinyl group, -CHO,



or
$-CH(OX)CH_2OX$, where X is H or $-C(O)-(C_1-C_3)$-alkyl and R_5 denotes H, OH or $O-(C_1-C_3)$-alkyl and the pharmaceutically acceptable salts thereof.

3. A process as claimed in claim 1, wherein the compounds of group A) are selected from the group of compounds of formula I as claimed in claim 2, which are characterized by at least one of the following attributes:
R denotes H or OH,
R_1 - R_3 denote independently from each other H or
$-\overset{O}{\overset{\|}{C}}-(C_1-C_3)$-alkyl or all three, two or one of the substituents R_1 - R_3 denote the group of formula II, as described above, in which n is an integer from 0 to 5 and the other(s) denote H,
R_6 and R_7 represent H or R_6 represents hydrogen and R_7 represents (C_1-C_4)-alkyl,
R_8 represents (C_1-C_{10})-alkyl and
R_9 represents cyclohexyl or R_8 and R_9 together with the N-atom to which they are attached represent the piperidino, morpholino, thiomorpholino, piperazino, imidazole, theophyllino or pyrrolidino radical,
R_4 denotes vinyl or $CHOHCH_2OH$ and
R_5 denotes H.

4. A process as claimed in claim 1, wherein the compounds of group B) are selected from the compounds characterized by the formula III



(III)

in which
R^1, R^4 and R^5, which may be the same or different, stand for hydrogen, hydroxy, lower alkoxy, dialkylphosphinylalkoxy, acyloxy or halogen, two of the radicals R^1, R^4 or R^5, when in adjacent positions and taken together, may form a methylenedioxy or ethylenedioxy group,
R^2 and R^3, which may be the same or different, stand for hydrogen, hydroxy, lower alkoxy, amino, alkylamino, dialkylamino, arylamino, amino or alkyl substituted by a 5- or 6-membered carbon ring containing up to 3 hetero atoms selected from the group of N, O and S; alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, acyl and optionally substituted aryl, aryl denoting an aromatic hydrocarbon radical having up to 10 carbon atoms;
R^2 represents a pair of electrons if R^6 stands for one of the radicals defined below and
R^2 and R^3 when taken together with the nitrogen atom to which they are bound may form an optionally substituted nitrogen heterocycle possibly containing a further nitrogen or oxygen atom, and
R^6 stands for hydrogen, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoal-

kyl, aralkyl, heterocyclically substituted alkyl, dialkylphosphinylalkyl, acyl and optionally substituted aryl or R^6 represents a pair of electrones if R^2 represents one of the radicals defined above;
and the acid addition salts and quaternary ammonium salts thereof.

5. A process as claimed in claim 1, wherein the compounds of group B) are selected from the following compounds:
9,10-dimethoxy-2-tert.-butylamino-6,7.dihydro-4H-pyrimido(6,1-a)isoquinoline-4-one hydrochloride,
9,10-dimethoxy-2-(2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride dihydrate,
9,10-dimethoxy-3-methyl-2-mesitylimino-2,3,6,7-tetrahydro4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-2-(N-methyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-3-isopropyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-2-(N-isopropyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-3-ethyl-2-mesitylimino-2,3,6,7-tetra hydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-2-(n-ethyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-3-acetyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one or
9,10-dimethoxy-2-(N-acetyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one.

6. A process as claimed in claim 1 containing 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one and 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride.

7. The use of a pharmaceutical composition as prepared according to one or more of claims 1 - 6 for hair growth and for arrest of hair loss.

8. The use of a pharmaceutical composition as prepared according to one or more of claims 1 - 6 for the treatment of androgenetic alopecia, alopecia areata and alopecia totalis.

9. Pharmaceutical composition as claimed in one or more of claims 1 - 6 for topical administration.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 12 1171

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
	No relevant documents have been disclosed.		A 61 K 7/06 A 61 K 31/505// (A 61 K 31/505 A 61 K 31:35)

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	29-01-1990	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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E : earlier patent document, but published on, or after the filing date
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& : member of the same patent family, corresponding document

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Office européen des brevets

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(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification : **09.09.92 Bulletin 92/37**

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(21) Application number : **89121171.6**

(22) Date of filing : **16.11.89**

(54) **Pharmaceutical compositions comprising labdane diterpenoid derivatives and pyrimido(6,1-a) isoquinolin-4-one derivatives and their use.**

(30) Priority : **19.11.88 EP 88119255**

(43) Date of publication of application : **30.05.90 Bulletin 90/22**

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(84) Designated Contracting States : **AT BE CH DE ES FR GB GR IT LI LU NL SE**

(56) References cited :
- -

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EP 0 370 379 B1

Description

The invention described herein relates to pharmaceutical compositions comprising at least one substance selected from the group of compounds named labdane diterpenoid derivatives and at least one substance selected from the group of pyrimido(6,1-a)isoquinoline-4-one derivatives.

Said pharmaceutical compositions can be used for increasing the rate of terminal hair growth, for stimulating the conversion of vellus hair to growth as terminal hair and for arresting the loss of hair as potential methods for the treatment of alopecia.

Alopecia or Baldness is an affliction resulting from loss of hair. Different types of hair loss (alopecia areata, alopecia totalis, androgenetic alopecia) are recognised by dermatologists, the most common by far being known as androgenetic alopecia or male pattern alopecia or baldness. While this type of hair loss is largely confined to males, it is not unknown in women. The condition of alopecia or baldness is a consequence of a combination of factors:

(1) transition of hairs from terminal to vellus,

(2) increased number of telogen hairs - some of which have been shed, and

(3) loss of hair follicles.

Very little is known about the cause of male pattern baldness, although it is felt that it could be genetic or hormonal in origin. At the present time, the treatment of male pattern alopecia is attempted either through non-drug related approaches such as hair transplantation, ultra-violet radiation massage, psychiatric treatment and exercise therapy or through drug therapy. The non-drug related approaches to the problem are stated to be either generally ineffective or in the case of transplantation too costly, time-consuming and impractical. In the case of drug therapy, many types of therapeutic drugs ranging from vitamins to hormones, or diphenylhydantoin or streptomycin have been tried and only recently there has been an indication of moderate success. Among treatments which have shown some promise to have grown hair through topical application to the scalp of a human being suffering from male pattern baldness are the use of a microemulsion cream containing estradiol and oxandrolone or organic silicon or minoxidil.

Furthermore, the use of pyrimido(6,1-a)isoquinolin-4-one derivatives for the treatment of alopecia has already been proposed in the German patent application P 38 16 995.9.

Surprisingly, it has now been found that a pharmaceutical composition containing at least one diterpenoid derivative and at least one pyrimido(6,1-a)isoquinolin-4-one derivative is effective for increasing the rate of terminal hair growth, stimulating the conversion of vellus hair to growth as terminal hair and for arresting hair loss. Thus, said pharmaceutical composition is qualified for example for the treatment of alopecia, in particular for the treatment of the male pattern alopecia.

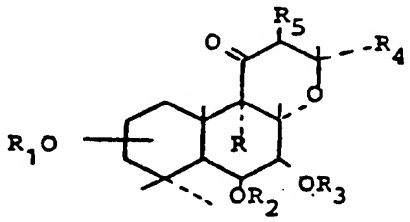
The instant invention relates to a pharmaceutical composition containing at least one compound of group A) consisting of labdane diterpeniods and at least one compound of group B) consisting of pyrimido(6,1-a(isoquinolin-4-one derivatives.

Labdane diterpeniod derivatives, for which a compound named Forskolin isolated from Coleus forskolii (Bhat, Bajura, Dornauer, de Souza, Fehlhaber, Tetrahedron Lett., 1669 (1977), Medicinal Research Reviews, Vol. 3, No. 2, 201 - 219 (1983)) is an example, are described in the following patents and patent applications:

a) Deutsche Offenlegungsschrift		2 557 784
"	"	2 654 796
"	"	3 502 686
"	"	3 502 685
"	"	3 535 086
Deutsche Patentanmeldung		37 18 589
"	"	37 30 748
Indian Patent		147 007
"	"	148 680
Indian Patent Application		345/BOM/84
"	"	346/BOM/84
"	"	122/BOM/85
"	"	50/BOM/87
"	"	51/BOM/87
"	"	238/BOM/87
"	"	265/BOM/87
"	"	266/BOM/87

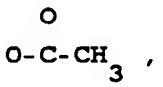
The compounds, in particular the compounds of the examples of said patents patent applications are preferred compounds of group A) of the instant application.

Further preferred compounds of group A) are selected from the compounds characterized by formula I

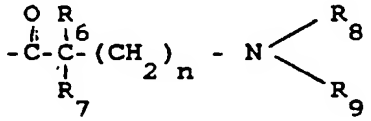


(I)

wherein R denotes H, OH, O-(C_1-C_3)-alkyl or

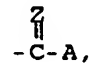


R_1 - R_3 denote independently from each other H, (C_1 -C_6)-alkyl, (C_1-C_6)-alkenyl, (C_1-C_6)-alkynyl, (C_3-C_8)-cycloalkyl, dialkylamino or aralkyl in which the alkyl groups have at most 4 carbon atoms, (C_1-C_{20})-acyl, (C_2-C_{10})-alkoxycarbonyl, (C_2-C_{10})-arylaminocarbonyl or either all three or only two or one of the substituents R_1, R_2 and R_3 denote the radical of formula II

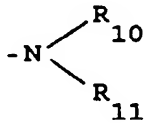


(II)

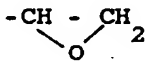
and the other or others hydrogen, where
R_6 and R_7 are identical or different and represent hydrogen, (C_1-C_6)-alkyl or an aryl radical,
n stands for 0 or an integer from 1 to 10,
R_8 denotes hydrogen if R_9 represents hydrogen, unsubstituted or substituted (C_1-C_6)-alkyl, (C_5-C_7)-cycloalkyl, aryl-(C_1-C_2)-alkyl, aryl, a heterocyclic hydrocarbon wherein the heteroatoms may be oxygen, nitrogen or sulfur, optionally substituted amino, hydroxyl, acyl, di-(C_1-C_6)-alkylamino, carbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyl-(C_1-C_6)-alkyl, or
R_8 and R_9 have the same meaning and stand for optionally substituted (C_1-C_6)-alkyl, aryl, or aryl-(C_1-C_2)-alkyl, or
R_8 denotes (C_1-C_6)-alkyl and R_9 represents substituted (C_1-C_6)-alkyl, (C_5-C_7)-cycloalkyl, aryl-(C_1-C_6)-alkyl or di-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl, or
R_8 and R_9 together with the N-atom to which they are attached represent a heterocyclic hydrocarbon which in addition to the N-atom may contain one or more heteroatoms from the group comprising nitrogen, oxygen and sulfur and may be singly or multiply substituted by (C_1-C_6)-alkyl, aryl-(C_1-C_6)-alkyl, hydroxy-(C_1-C_6)-alkyl, aryl, hydroxyl or further heterocyclic hydrocarbons, or
R_1, R_2 and/or R_3 denote



in which Z represents oxygen or sulfur,
and A either represents the radical



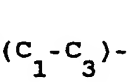
in which R_{10} represents hydrogen or (C_1-C_6)-alkyl, and
R_{11} represents (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, aryl, aryl-(C_1-C_6)-alkyl, (C_2-C_6)-carbalkoxy or sulfonylaryl, or
R_{10} and R_{11}, together with the nitrogen atom to which they are bonded, form a heterocycle which may contain as further heteroatom oxygen, nitrogen or sulfur, or A represents the radical $-OR_{12}$ in which
R_{12} represents (C_1-C_6)-alkyl or halogeno-(C_1-C_6)-alkyl, or
R_1 represents a tris-(C_1-C_6)-alkyl-silyl group, and
R_2 and R_3 have the meanings given above,
R_4 denotes ethyl, a vinyl group,-CHO,



or $-CH(OX)CH_2OX$, where X is H or -C(O)-(C_1-C_3)-alkyl and
R_5 denotes H, OH or O-(C_1-C_3)-alkyl and the pharmaceutically accpetable salts thereof.

Particularly preferred pharmaceutical compositions are those, wherein the compounds of group A) are selected from the group of compounds of formula I as described above, which are characterized by at least one of the following attributes:

R denotes H or OH,
R_1 - R_3 denote independently from each other H or



alkyl or either all three, two or one of the substituents R_1 - R_3 denote the group of formula II, as described above,

in which n is an integer from 0 to 5, and the other(s) denote H,

R_6 and R_7 represent H or R_6 represents hydrogen and R_7 represents (C_1-C_4)-alkyl,

R_8 represents (C_1-C_{10})-alkyl and

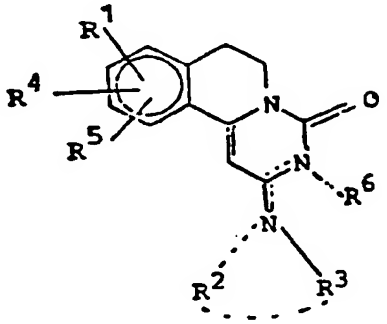
R_9 represents cyclohexyl or R_8 and R_9 together with the N-atom to which they are attached represent the piperidino, morpholino, thiomorpholino, piperazino, imidazole, theophyllino or pyrrolidino radical,

R_4 denotes vinyl or $CHOHCH_2OH$ and

R_5 denotes H.

Many from the compounds of group A) may form salts from organic or inorganic acids. Suitable examples of salts from organic or inorganic acids are hydrochloride, hydrobromide, sulfate, phosphate, acetate, oxalate, tartrate, citrate, maleate or fumarate.

The compounds of group B) for which Trequinsin (cf. IRCS Med. Sci. 1981, 9, 325; Life Sci., 1984, 31, 2037; Naunyn-Schmiedeberg's Arch. Pharmacol., 1982, 319, Suppl. R49) is an example, are explicitly described in b) Deutsche Offenlegungsschriften 27 20 085 and 28 01 289 and in the Indian patents 147 624, 149 432 and 149 457. Preferred compounds are described and exemplified in the patent applications cited under b). Further preferred compounds of group B) are characterized by the formula III



III

in which

R^1, R^4 and R^5, which may be the same or different, stand for hydrogen, hydroxy, lower alkoxy, dialkylphosphinylalkoxy, acyloxy or halogen,

two of the radicals R^1, R^4 or R^5, when in adjacent positions and taken together, may form a methylenedioxy or ethylenedioxy group,

R^2 and R^3, which may be the same or different, stand for hydrogen, hydroxy, lower alkoxy, amino, alkylamino, dialkylamino, arylamino, amino or alkyl substituted by a 5-or 6-membered carbon ring containing up to 3 hetero atoms selected from the group of N, O and S; alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, acyl and optionally substituted aryl, aryl denoting an aromatic hydrocarbon radical having up to 10 carbon atoms;

R^2 represents a pair of electrons if R^6 stands for one of the radicals defined below and

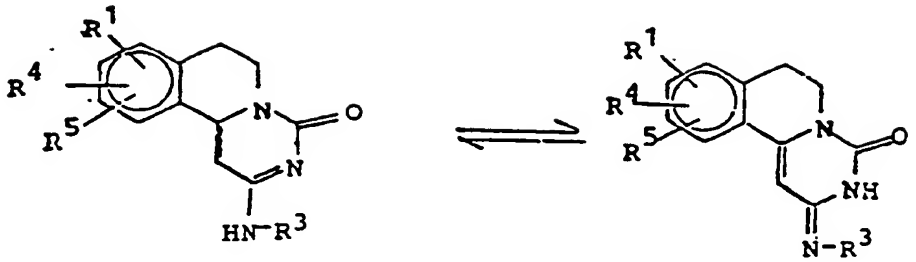
R^2 and R^3 when taken together with the nitrogen atom to which they are bound may form an optionally substituted nitrogen heterocycle possibly containing a further nitrogen or oxygen atom, and

R^6 stands for hydrogen, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, heterocyclically substituted alkyl, dialkyl-phosphinylalkyl, acyl and optionally substituted aryl or

R^6 represents a pair of electrones if R^2 represents one of the radicals defined above;

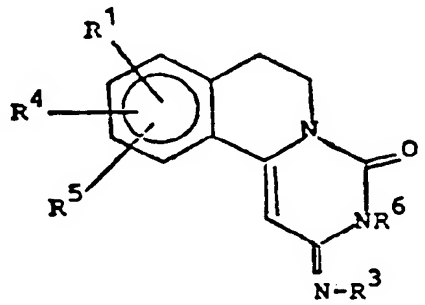
and the acid addition salts and quaternary ammonium salts thereof.

In the case of at least one of the two radicals R^2 and R^3 being hydrogen, the above definition of the pyrimido(6,1-a)isoquinolin-4-one derivatives also encompass the isomers of the following formula Ib, obtained by complete isomerization of compounds of formula Ia or being in equilibrium with the compounds of formula Ia.



Ia Ib

The definition of the pyrimido(6,1-a)isoquinolin-4-one derivatives also encompass the isomer of formula Ic



Ic

in which R^1, R^3, R^4, R^5 and R^6 have the above meanings.

If R^1, R^2, R^3, R^4 and R^5 stand for lower alkoxy groups, those having up to 3 carbon atoms are suitable.

Suitable acyloxy radicals for R^1, R^4 or R^5 are those in which the acyl group is linear or branched (C_1-C_6)-alkanoyl, for example acetyl, or aroyl, especially benzoyl in which the phenyl nucleus may be substituted one to three times by halogen, nitro, hydroxy, (C_1-C_3)-alkoxy and (C_1-C_3)-alkyl.

If R^1, R^4 or R^5 stand for halogen, chlorine is preferred. Suitable dialkylphosphinylalkoxy radicals for R^1, R^4 or R^5 are those in which the alkyl and alkoxy groups carry at most 3 carbon atoms, for example dimethylphosphinylmethoxy.

Especially suitable alkylamino or dialkylamino radicals for R^2 or R^3 are those in which the alkyl groups have at most 3 carbon atoms, for example methylamino or dimethylamino.

Suitable arylamino radicals for R^2 or R^3 are phenylamino radicals in which the phenyl residue may be substituted one or several times by halogen, for example chlorine, (C_1-C_3)-alkyl, for example methyl, or nitro. A suitable nitrogen-containing heterocyclic amino radical for R^2 or R^3 is, for example, the N-morpholinoamino radical.

As alkyl radical for R^2, R^3 or R^6 there can be used those having at most 6 carbon atoms, for example methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec.butyl or tert.butyl.

Suitable cycloalkyl radicals for R^2, R^3 and R^6 are those having at most 6 carbon atoms, for example cyclohexyl.

In the case of R^2, R^3 or R^6 being a substituted alkyl radical there may be used those having up to 6 carbon atoms and substituted by one or two hydroxy or (C_1-C_3)-alkoxy groups, halogen atoms, for example chlorine, amino or di-(C_1-C_4)-alkyl-amino, dialkylphosphinylalkyl, for example dimethylphosphinylmethyl.

Examples of aralkyl radical for R^2, R^3 and R^6 are those having at most 8 carbon atoms, in which the aryl radical may be mono- or polysubstituted, especially substituted one, two, or three times by the substituents

defined above for R^1.

Suitable heterocyclic alkyl radicals for R^2, R^3 and R^6 are, for example, furfuryl and tetrahydrofurfuryl.

Suitable examples of aryl radicals for R^2, R^3 and R^6 are phenyl radicals optionally substituted one or several times, preferably one, two or three times by halogen, for example fluorine, chlorine and bromine, (C_1-C_3)-alkyl and (C_1-C_3)-alkoxy, for example methyl, ethyl, methoxy and ethoxy, haloalkyl, for example trifluoromethyl, amino or hydroxy, in the latter the hydrogen atoms possibly being replaced by an alkali metal, for example sodium.

Suitable nitrogen-containing heterocyclic radicals are, for example, pyrrolidino, piperidino, morpholino, and piperazino, optionally substituted by alkyl, alkoxycarbonyl, aryl or a nitrogen heterocycle, the terms alkyl, alkoxy, aryl and nitrogen heterocycle having the above meaning.

Examples of suitable acyl radicals for R^2, R^3 and R^6 are linear or branched (C_1-C_6)-alkanoyl, such as acetyl, or aroyl, such as benzoyl, wherein the phenyl residue may be substituted one or several times by the substituents defined above for R^2, R^3 and R^6 when they represent an aryl radical.

As salts of the pyrimido(6,1-a)isoquinolin-4-one derivatives of the invention there are mentioned by way of example those of inorganic or organic acids, for example the hydrochlorides, hydrobromides, sulfates, phosphates, acetates, oxalates, tartrates, citrates, maleates or fumarates.

Suitable quaternary ammonium salts of the pyrimido(6,1-a)-isoquinolin-4-one derivatives of the invention are, for example, the salts derived from alkyl halides, such as methiodides.

Preferred substituents are:

alkoxy for R^1 and R^4, hydrogen for R^5, (C_1-C_6)-alkyl or phenyl optionally substituted one to three times as defined above for R^2, hydrogen, (C_1-C_6)-alkyl, cycloalkyl, substituted alkyl, aralkyl, heterocyclic alkyl, substituted aryl and (C_1-C_6)-alkanoyl for R^3 and R^6.

Particularly preferred compounds are:

9,10-dimethoxy-2-tert.-butylamino-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoline-4-one hydrochloride,

9,10-dimethoxy-2-(2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)-isoquinolin-4-one hydrochloride dihydrate,

9,10-dimethoxy-3-methyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-2-(N-methyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-3-isopropyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-2-(N-isopropyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-3-ethyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-2-(N-ethyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-3-acetyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one and

9,10-dimethoxy-2-(N-acetyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one.

The production of the compounds of groups A) and B) is explicitly described in the patents and patent applications cited above under a) and b).

A pharmaceutical composition with extraordinary activity contains 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one and 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a) isoquinolin-4-one hydrochloride.

Detailed investigations have shown that the combined topical administration of at least one compound of group A) and at least one compound of group B) results in an activity on hair growth which is far in excess of that which would result when said compounds are used singly; thus, said combinations show a clear synergistic effect. An important advantage of the pharmaceutical compositions according to the instant invention is the fact that the compounds of group A) and group B) have an influence on hair growth through different mechanisms.

The pharmaceutical compositions according to the instant invention can be administered to any mammals, however, they have a special importance for the human being.

For the increase of hair growth and for the treatment of alopecia (e.g. alopecia areata, alopecia totalis or androgenetic alopecia) a combination of one or more compounds of group A) and one or more compounds of group B) is administered, preferably topically, optionally together with suitable carriers and/or excipients. Examples of application forms which may be mentioned are solutions, suspensions, emulsions, pastes, ointments, soaps, jellies, creams, lotions, dusting powders, surfactant cotaing cleansing products, oils, sprays, aerosols and the like.

Any desired carriers and/or excipients are added to the pharmaceutical composition. Excipients which are to be preferred are derived from the group of preservatives, antioxidants, stabilizers, solubilizers, vitamins, colorants and odor improvers.

Ointments, pastes, creams and jellies can, besides the active substance(s), contain the customary excipients, for example animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonite, silica, talc and zinc oxide, or mixtures of these substances.

Dusting powders and sprays can, besides the active substance(s), contain the customary excipients, for example lactose, talc silica, aluminum hydroxide, calcium silicate and polyamide powder, or mixtures of these substances. Sprays can additionally contain the customary propellants, for example chlorofluorohydrocarbons, propane/butane or dimethyl ether.

Solutions and emulsions can, besides the active substance(s), contain the customary excipients such as solvents, solubilizers and emulsifiers, for example water, ethanol, isopropanol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylen glycol, dimethylacetamide, 1,3-butylglycol, oils, especially cottonseed oil, peanut oil, corn oil, olive oil, castor oil and sesame oil, glycerol fatty acid esters, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances.

Suspensions can, besides the active substance(s), contain the customary excipients such as liquid diluents, for example water, ethanol or propylene glycol, suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances.

Soaps can, besides the active substance(s), contain the customary excipients such as, for example, alkali metal salts or fatty acids, salts of fatty acid hemiesters, fatty acid protein hydrolyzates, isethionates, lanolin, fatty alcohols, vegetable oils, plant extracts, glycerol, sugar, or mixtures of these substances.

Surfactant-containing cleansing products can, besides the active substance(s), contain the customary excipients such as, for example, salts of fatty alcohol sulfates, fatty alcohol ether sulfates, sulfosuccinic hemiesters, fatty acid protein hydrolyzates, isethionates, imidazolinium derivatives, methyllaurates, sarcosinates, fatty acid amide ether sulfates, alkylamidobetaines, fatty alcohols, fatty acid glycerides, fatty acid diethanolamides, vegetable and synthetic oils, lanolin derivatives, ethoxylated glycerol fatty acid esters, or mixtures of these substances.

Oils can, besides the active substance(s), contain the customary excipients such as, for example, synthetic oils such as fatty acid esters, fatty alcohols, silicone oils, neutral oils such as vegetable oils, and oily plant extracts, liquid paraffins, lanolin oil, or mixtures of these substances.

A physiologically effective amount of a pharmacologically acceptable composition is applied to the scalp as often as required. A preferred concentration of the compounds of group A) and the compounds of group B) in combination, when administered as topical solution to the scalp is in the range of 0.1 % to 5 %.

The particularly preferred range of concentration is 0.5 - 3 %. The ratio of the compounds of group A) to the compounds of group B) may vary from 1:99 to 99:1. The preferred solvents for solutions are such as water, ethanol, propylene glycol, dimethylacetamide, used singly or in combination in appropriate proportion to keep the active ingredients in solution. The number of administrations per day to the deltoid areas is dependent on the concentration of the active ingredient(s) administered. Application of the solutions may be made by way of contact occlusion to the deltoid areas. Occlusion of the solution may be obtained by any conventional means such as bandages, plastic coverings, shower caps, swimming caps etc.

The following examples illustrate the invention.

Example 1:

One thousand ml of an aqueous solution containing 2 % 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride and 2 % 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one is prepared from the following types and amount of ingredients.

9,10-Dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)-isoquinolin-4-one hydrochloride	20 g
7β-Acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one	20 g
Propylene glycol	250 g
Polyethylene glycol	400 g
Ethyl alcohol	300 g
Dionised water q.s. ad	1000 ml

The ingredients 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride and 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one are dissolved separately into propylene glycol and polyethylene glycol maintaining the temperature of 35 - 45°C. The solutions are then cooled to room temperature and mixed under stirring and further diluted with ethanol first and then with water to make the volume of the solution to 1000 ml. The resulting solution is sterilised by filtration. The solution is then filled aseptically into sterile containers.

Example 2:

A solution containing 1 % 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride and 1 % 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one is prepared from the following amount of ingredients

9,10-Dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)-isoquinolin-4-one hydrochloride (Trequisin)	1 g
7β-Acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one (Forskolin)	1 g
Propylene glycol	40 ml
Ethyl alcohol q.s.ad	100 ml

The ingredients 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride and 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one are dissolved in propylene glycol at room temperature under stirring and further diluted with ethanol to make the volume of the solution to 100 ml. The resulting solution is sterilised by filtration. The solution is then filled aseptically into sterile containers.

The solutions were also prepared similarly using tetraglycol in place of a mixture of polyethylene glycol and propylene glycol in the above example.

The solutions so prepared can be used in the topical application for treatment of male pattern baldness by application to the affected area of the scalp daily.

Detection of hair growth-promoting effect of Forskolin + Trequisin.

Male and female rabbits having a weight of 500 - 700 g and an age of 5 - 6 weeks were used for the experiments. The animals were kept with the mother during the entire experiment.

The rear part of the experimental animals was shaved in four sites (two on each side) using electric hair clippers. Each animal had 4 shaved sites of 3 cm^2 each. 18 hours after shaving, 0.2 ml of test solution (see Example 2) and also solvent as a blank sample were placed on each shaved site and massaged in for about 60 sec. The application was repeated daily and at the end of each week in each case 10 hairs were pulled out from each site and their length was determined.

Solution of a mixture of Trequisin and Forskolin having a content of 1 % of each active compound was used. Results obtained are shown in Table 1.

Table 1

Hair growth in mm in rabbits under the influence of treatment with a solution containing Trequisin and Forskolin

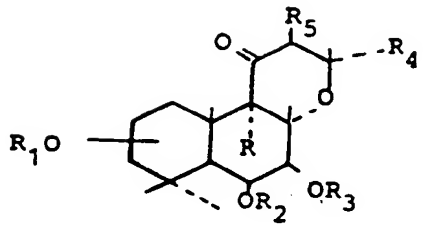
Treatment period in weeks	Solvent	Solution containing Trequisin + Forskolin
1	9.88 ± 0.38	10.32 ± 0.49
4	13.78 ± 0.91	15.38 ± 0.91
5	19.10 ± 0.88	22.26 ± 0.89

Claims

Claims for the following Contrating States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

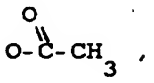
1. A pharmaceutical composition containing at least one compound of group A) consisting of labdane diterpenoid derivatives and at least one compound of group B) consisting of pyrimido(6,1-a)isoquinolin-4-one derivatives.

2. A pharmaceutical composition as claimed in claim 1, wherein the compounds of group A) are selected from the compounds characterized by the formula I

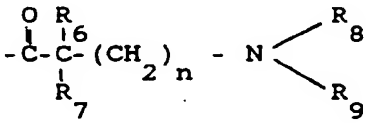


(I)

wherein R denotes H, OH, O-(C_1-C_3)-alkyl or



R_1 - R_3 denote independently from each other H, (C_1-C_6)-alkyl, (C_1-C_6)-alkenyl, (C_1-C_6)-alkynyl, (C_3-C_8)-cycloalkyl, dialkylamino or aralkyl in which the alkyl groups have at most 4 carbon atoms, (C_1-C_{20})-acyl, (C_2-C_{10})-alkoxycarbonyl, (C_2-C_{10})-arylaminocarbonyl or either all three or only two or one of the substituents R_1, R_2 and R_3 denote the radical of formula II

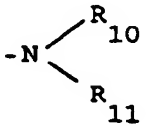


(II)

and the other or others hydrogen, where R_6 and R_7 are identical or different and represent hydrogen, (C_1-C_6)-alkyl or an aryl radical, n stands for 0 or an integer from 1 to 10, R_8 denotes hydrogen if R_9 represents hydrogen, unsubstituted or substituted (C_1-C_6)-alkyl, (C_5-C_7)-cycloalkyl, aryl-(C_1-C_2)-alkyl, aryl, a heterocyclic hydrocarbon wherein the heteroatoms may be oxygen, nitrogen or sulfur, optionally substituted amino, hydroxyl, acyl, di-(C_1-C_6)alkylamino, carbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)alkylcarbonyl-(C_1-C_6)-alkyl, or R_8 and R_9 have the same meaning and stand for optionally substituted (C_1-C_6)-alkyl, aryl, or aryl-(C_1-C_2)-alkyl, or R_8 denotes (C_1-C_6)-alkyl and R_9 represents substituted (C_1-C_6)-alkyl, (C_5-C_7)-cycloalkyl, aryl-(C_1-C_6)-alkyl or di-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl, or R_8 and R_9 together with the N-atom to which they are attached represent a heterocyclic hydrocarbon which in addition to the N-atom may contain one or more heteroatoms from the group comprising nitrogen, oxygen and sulfur and may be singly or multiply substituted by (C_1-C_6)-alkyl, aryl-(C_1-C_6)-alkyl, hydroxy-(C_1-C_6)-alkyl, aryl, hydroxyl or further heterocaclic hydrocarbons, or

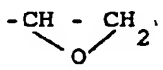
R_1, R_2 and/or R_3 denote

in which Z represents oxygen or sulfur,
and A either represents the radical



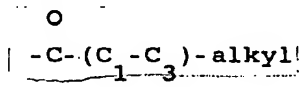
in which R_{10} represents hydrogen or (C_1-C_6)-alkyl, and R_{11} represents (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, aryl, aryl-(C_1-C_6)-alkyl, (C_2-C_6)-carbalkoxy or sulfonylaryl, or R_{10} and R_{11}, together with the nitrogen atom to which they are bonded, form a heterocycle which may contain as further heteroatom oxygen, nitrogen

or sulfur, or A represents the radical $-OR_{12}$ in which R_{12} represents (C_1-C_6)-alkyl or halogeno-(C_1-C_6)-alkyl, or R_1 represents a tris-(C_1-C_6)-alkyl-silyl group, and
R_2 and R_3 have the meanings given above,
R_4 denotes ethyl, a vinyl group, -CHO,



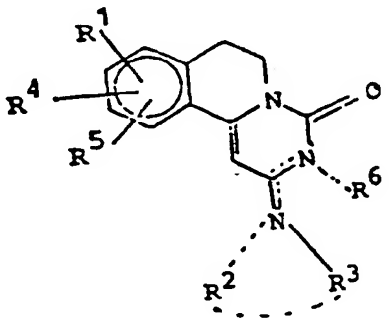
or $-CH(OX)CH_2OX$, where X is H or $-C(O)-(C_1-C_3)$-alkyl and R_5 denotes H, OH or $O-(C_1-C_3)$-alkyl and the pharmaceutically acceptable salts thereof.

3. A pharmaceutical composition as claimed in claim 1, wherein the compounds of group A) are selected from the group of compounds of formula I as claimed in claim 2, which are characterized by at least one of the following attributes:
R denotes H or OH,
R_1 - R_3 denote independently from each other H or



or all three, two or one of the substituents R_1 - R_3 denote the group of formula II, as described above, in which n is an integer from 0 to 5 and the other(s) denote H,
R_6 and R_7 represent H or R_6 represents hydrogen and R_7 represents (C_1-C_4)-alkyl,
R_8 represents (C_1-C_{10})-alkyl and
R_9 represents cyclohexyl or R_8 and R_9 together with the N-atom to which they are attached represent the piperidino, morpholino, thiomorpholino, piperazino, imidazole, theophyllino or pyrrolidino radical,
R_4 denotes vinyl or $CHOHCH_2OH$ and
R_5 denotes H.

4. A pharmaceutical composition as claimed in claim 1, wherein the compounds of group B) are selected from the compounds characterized by the formula III



(III)

in which
R^1, R^4 and R^5, which may be the same or different, stand for hydrogen, hydroxy, lower alkoxy, dialkylphosphinylalkoxy, acyloxy or halogen, two of the radicals R^1, R^4 or R^5, when in adjacent positions and taken together, may form a methylenedioxy or ethylenedioxy group,
R^2 and R^3, which may be the same or different, stand for hydrogen, hydroxy, lower alkoxy, amino, alkylamino, dialkylamino, arylamino, amino or alkyl substituted by a 5- or 6-membered carbon ring containing up to 3 hetero atoms selected from the group of N, O and S; alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, acyl and optionally substituted aryl, aryl denoting an aromatic hydrocarbon radical having up to 10 carbon atoms;
R^2 represents a pair of electrons if R^6 stands for one of the radicals defined below and

R^2 and R^3 when taken together with the nitrogen atom to which they are bound may form an optionally substituted nitrogen heterocycle possibly containing a further nitrogen or oxygen atom, and
R^6 stands for hydrogen, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, heterocyclically substituted alkyl, dialkylphosphinylalkyl, acyl and optionally substituted aryl or
R^6 represents a pair of electrones if R^2 represents one of the radicals defined above;
and the acid addition salts and quaternary ammonium salts thereof.

5. A pharmaceutical composition as claimed in claim 1, wherein the compounds of group B) are selected from the following compounds:
9,10-dimethoxy-2-tert.-butylamino-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoline-4-one hydrochloride,
9,10-dimethoxy-2-(2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride dihydrate,
9,10-dimethoxy-3-methyl-2-mesitylimino-2,3,6,7-tetrahydro4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-2-(N-methyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-3-isopropyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-2-(N-isopropyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-3-ethyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-2-(n-ethyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-3-acetyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one or
9,10-dimethoxy-2-(N-acetyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one.

6. A pharmaceutical composition as claimed in claim 1 containing
7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one and 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride.

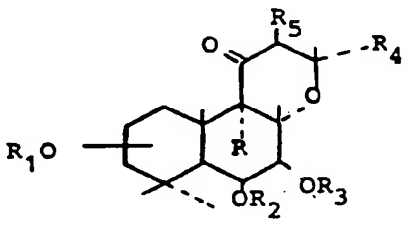
7. Pharmaceutical composition as claimed in one or more of claims 1 - 6 for topical administration.

8. Process for the production of a pharmaceutical composition as claimed in claims 1 - 6 or 9, wherein at least one compound of group A) and at least one compound of group B) are, together with acceptable carriers and/or excipients, transformed into a form suitable for administration.

Claims for the following Contracting States : ES, GR

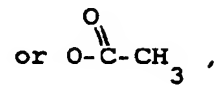
1. A process for the preparation of a pharmaceutical composition wherein at least one compound of group A) consisting of labdane diterpenoid derivatives and at least one compound of group B) consisting of pyrimido(6,1-a)isoquinolin-4-one derivatives are transformed into a form suitable for administration

2. A process as claimed in claim 1, wherein the compounds of group A) are selected from the compounds characterized by the formula I

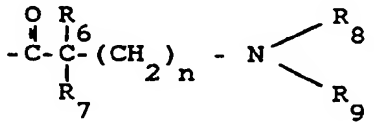


(I)

wherein R denotes H, OH, O-(C_1-C_3)-alkyl or



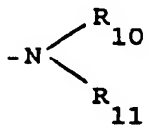
R_1 - R_3 denote independently from each other H, (C_1-C_6)-alkyl, (C_1-C_6)-alkenyl, (C_1-C_6)-alkynyl, (C_3-C_8)-cycloalkyl, dialkylamino or aralkyl in which the alkyl groups have at most 4 carbon atoms, (C_1-C_{20})-acyl, (C_2-C_{10})-alkoxycarbonyl, (C_2-C_{10})-arylaminocarbonyl or either all three or only two or one of the substituents R_1, R_2 and R_3 denote the radical of formula II



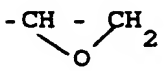
(II)

and the other or others hydrogen, where R_8 and R_7 are identical or different and represent hydrogen, (C_1-C_6)-alkyl or an aryl radical, n stands for 0 or an integer from 1 to 10, R_9 denotes hydrogen if R_9 represents hydrogen, unsubstituted or substituted (C_1-C_6)-alkyl, (C_5-C_7)-cycloalkyl, aryl-(C_1-C_2)-alkyl, aryl, a heterocyclic hydrocarbon wherein the heteroatoms may be oxygen, nitrogen or sulfur, optionally substituted amino, hydroxyl, acyl, di-(C_1-C_6)alkylamino, carbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)alkylcarbonyl-(C_1-C_6)-alkyl, or R_8 and R_9 have the same meaning and stand for optionally substituted (C_1-C_6)-alkyl, aryl, or aryl-(C_1-C_2)-alkyl, or R_8 denotes (C_1-C_6)-alkyl and R_9 represents substituted (C_1-C_6)-alkyl, (C_5-C_7)-cycloalkyl, aryl-(C_1-C_6)-alkyl or di-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl, or R_8 and R_9 together with the N-atom to which they are attached represent a heterocyclic hydrocarbon which in addition to the N-atom may contain one or more heteroatoms from the group comprising nitrogen, oxygen and sulfur and may be singly or multiply substituted by (C_1-C_6)-alkyl, aryl-(C_1-C_6)-alkyl, hydroxy-(C_1-C_6)-alkyl, aryl, hydroxyl or further heterocaclic hydrocarbons, or
R_1, R_2 and/or R_3 denote

in which Z represents oxygen or sulfur,
and A either represents the radical

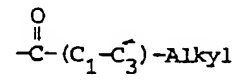


in which R_{10} represents hydrogen or (C_1-C_6)-alkyl, and R_{11} represents (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, aryl, aryl-(C_1-C_6)-alkyl, (C_2-C_6)-carbalkoxy or sulfonylaryl, or R_{10} and R_{11}, together with the nitrogen atom to which they are bonded, form a heterocycle which may contain as further heteroatom oxygen, nitrogen or sulfur, or A represents the radical -OR_{12} in which
R_{12} represents (C_1-C_6)-alkyl or halogeno-(C_1-C_6)-alkyl, or
R_1 represents a tris-(C_1-C_6)-alkyl-silyl group, and
R_2 and R_3 have the meanings given above,
R_4 denotes ethyl, a vinyl group, -CHO,



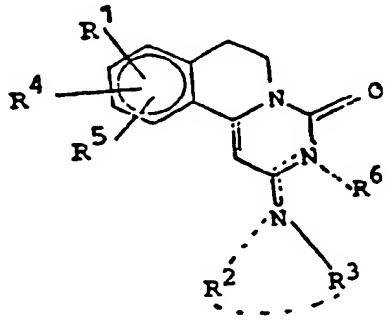
or
-CH(OX)CH_2OX , where X is H or -C(O)-(C_1-C_3)-alkyl and
R_5 denotes H, OH or O-(C_1-C_3)-alkyl and the pharmaceutically acceptable salts thereof.

3. A process as claimed in claim 1, wherein the compounds of group A) are selected from the group of compounds of formula I as claimed in claim 2, which are characterized by at least one of the following attributes:
R denotes H or OH,
R_1 - R_3 denote independently from each other H or



or all three, two or one of the substituents R_1 - R_3 denote the group of formula II, as described above, in which n is an integer from 0 to 5 and the other(s) denote H,
R_6 and R_7 represent H or R_6 represents hydrogen and R_7 represents (C_1-C_4)-alkyl,
R_8 represents (C_1-C_{10})-alkyl and
R_9 represents cyclohexyl or R_8 and R_9 together with the N-atom to which they are attached represent the piperidino, morpholino, thiomorpholino, piperazino, imidazole, theophyllino or pyrrolidino radical,
R_4 denotes vinyl or $CHOHCH_2OH$ and
R_5 denotes H.

4. A process as claimed in claim 1, wherein the compounds of group B) are selected from the compounds characterized by the formula III



(III)

in which
R^1, R^4 and R^5, which may be the same or different, stand for hydrogen, hydroxy, lower alkoxy, dialkylphosphinylalkoxy, acyloxy or halogen, two of the radicals R^1, R^4 or R^5, when in adjacent positions and taken together, may form a methylenedioxy or ethylenedioxy group,
R^2 and R^3, which may be the same or different, stand for hydrogen, hydroxy, lower alkoxy, amino, alkylamino, dialkylamino, arylamino, amino or alkyl substituted by a 5- or 6-membered carbon ring containing up to 3 hetero atoms selected from the group of N, O and S; alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, acyl and optionally substituted aryl, aryl denoting an aromatic hydrocarbon radical having up to 10 carbon atoms;
R^2 represents a pair of electrons if R^6 stands for one of the radicals defined below and
R^2 and R^3 when taken together with the nitrogen atom to which they are bound may form an optionally substituted nitrogen heterocycle possibly containing a further nitrogen or oxygen atom, and
R^6 stands for hydrogen, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, heterocyclically substituted alkyl, dialkylphosphinylalkyl, acyl and optionally substituted aryl or
R^6 represents a pair of electrones if R^2 represents one of the radicals defined above;
and the acid addition salts and quaternary ammonium salts thereof.

5. A process as claimed in claim 1, wherein the compounds of group B) are selected from the following compounds:
9,10-dimethoxy-2-tert.-butylamino-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoline-4-one hydrochloride,
9,10-dimethoxy-2-(2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride dihydrate,
9,10-dimethoxy-3-methyl-2-mesitylimino-2,3,6,7-tetrahydro4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-2-(N-methyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-3-isopropyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-2-(N-isopropyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-3-ethyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-2-(n-ethyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,
9,10-dimethoxy-3-acetyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one or
9,10-dimethoxy-2-(N-acetyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one.

6. A process as claimed in claim 1 containing 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-en-11-one and 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride.

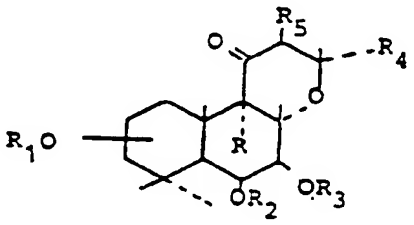
7. Pharmaceutical composition as claimed in one or more of claims 1 - 6 for topical administration.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

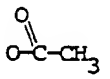
1. Pharmazeutische Zusammenzetzung mit einem Gehalt an wenigstens einer Verbindung aus Gruppe A), bestehend aus Labdanditerpenoidderivaten, und an weinigstens einer Verbindung aus Gruppe B), bestehend aus Pyrimido-(6,1-a)isochinolin-4-on-Derivaten.

2. Pharmazeutische Zusammensetzung nach Anspruch 1, worin die Verbindugen der Gruppe A) aus den durch die Formel I

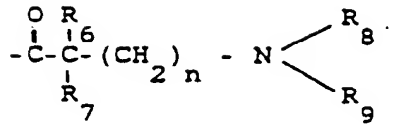


(I)

charakterisierten Verbindungen, in welcher Formel R für H, OH, O-(C_1-C_3)-Alkyl oder



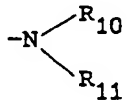
steht, R_1-R_3 unabhängig voneinander Wasserstoff, (C_1-C_6)-Alkyl, (C_1-C_6)-Alkenyl, (C_1-C_6)-Alkinyl, (C_3-C_8)--Cycloalkyl, Dialkylamino oder Aralkyl, worin die Alkylgruppen höchstens 4 Kohlenstoffatome aufweisen, (C_1-C_{20})-Acyl, (C_2-C_{10})-Alkoxycarbonyl oder (C_2-C_{10})-Arylaminocarbonyl bedeuten, oder entweder alle drei oder nur zwei oder einer der Substituenten R_1, R_2 und R_3 für einen Rest der Formel II



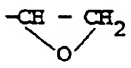
(II)

stehen und der oder die anderen Substituenten Wasserstoff bedeuten, worin R_6 und R_7 gleich oder verschieden sind und Wasserstoff, (C_1-C_6)-Alkyl oder einen Arylrest bedeuten, n für 0 oder eine ganze Zahl, von 1 bis 10 steht, R_8 Wasserstoff bezeichnet, wenn R_9 für Wasserstoff, unsubstituiertes oder substituiertes (C_1-C_6)-Alkyl, (C_5-C_7)-Cycloalkyl, Aryl-(C_1-C_2)-alkyl, Aryl, einer heterocyclischen Kohlenwasserstoff, worin die Heteroatome Sauerstoff, Stickstoff oder Schwefel sein können, gegebenenfalls substituiertes Amino, Hydroxyl, Acyl, Di-(C_1-C_6)alkyl-amino, Carbonyl, (C_1-C_6)-Alkoxycarbonyl, (C_1-C_6)-Alkylcarbonyl-(C_1-C_6)--alkyl steht, oder R_8 und R_9 die gleiche Bedeutung besitzen und für gegebenenfalls substituiertes (C_1-C_6)-Alkyl, Aryl oder Aryl-(C_1-C_2)--alkyl stehen, oder R_8 (C_1-C_6)-Alkyl bezeichnet und R_9 für substituiertes (C_1-C_6)-Alkyl, (C_5-C_7)-Cycloalkyl, Aryl-(C_1-C_6)-alkyl oder Di-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl steht, oder R_8 und R_9 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen heterocyclischen Kohlenwasserstoff bedeuten, der zusätzlich zu dem Stickstoffatom ein oder mehrere Heteroatome aus der Stickstoff, Sauerstoff und Schwefel umfassenden Gruppe enthalten kann und einfach oder mehrfach durch (C_1-C_6)-Alkyl, Aryl-(C_1-C_6)-alkyl, Hydroxy-(C_1-C_6)-alkyl, Aryl, Hydroxyl oder weitere heteroclyclische Kohlenwasserstoffe substituiert sein kann, oder R_1, R_2 und/oder R_3 für

stehen, worin Z Sauerstoff oder Schwefel bedeutet und A entweder einen Rest

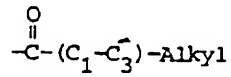


darstellt, worin R_{10} Wasserstoff oder (C_1-C_6)-Alkyl bedeutet und R_{11} (C_1-C_6)-Alkyl, (C_3-C_7)-Cycloalkyl, Aryl, Aryl-(C_1-C_6)-alkyl, (C_2-C_6)-Carbalkoxy oder Sulfonylaryl darstellt, oder R_{10} und R_{11}, gemeinsam mit dem Stickstoffatom, an das sie gebunden sind, einen Heterocyclus ausbilden, der als weiteres Heteroatom Sauerstoff, Stickstoff oder Schwefel enthalten kann, oder A den Rest -OR_{12} bedeutet, worin R_{12} für (C_1-C_6)-Alkyl oder Halogen-(C_1-C_6)-alkyl steht, oder R_1 eine Tris-(C_1-C_6)-alkyl-silylgruppe bedeutet, und R_2 und R_3 die oben angeführten Bedeutungen aufweisen, R_4 für Ethyl, eine Vinylgruppe, -CHO,



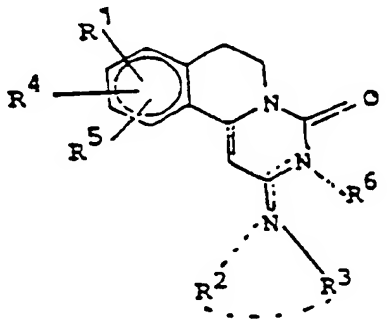
oder -CH(OX)CH_2OX steht, worin X Wasserstoff oder -C(O)-(C_1-C_3)-Alkyl ist und R_5 für Wasserstoff, OH oder O-(C_1-C_3)-Alkyl steht, und den pharmazeutisch annehmbaren Salzen hievon ausgewählt sind.

3. Pharmazeutische Zusammensetzung nach Anspruch 1, worin die Verbindungen der Gruppe A) aus der Gruppe von Verbindungen der Formel I, wie in Anspruch 2 beansprucht, ausgewählt sind, die durch wenigstens eines der folgenden Merkmale charakterisiert sind:
R steht für H oder OH,
R_1-R_3 bedeuten unabhängig voneinander Wasserstoff oder



oder alle drei, zwei oder einer der Substituenten R_1-C_3 bezeichnet die Gruppe der Formel II, wie vorstehend beschrieben, worin n eine ganze Zahl von 0 bis 5 ist und der oder die anderen Substituenten Wasserstoff darstellen,
R_6 und R_7 bedeuten Wasserstoff oder R_6 steht für Wasserstoff und R_7 bedeutet (C_1-C_4)-Alkyl,
R_8 bedeutet (C_1-C_{10})-Alkyl und
R_9 bedeutet Cyclohexyl oder R_8 und R_9, gemeinsam mit dem Stickstoffatom, an das sie gebunden sind, stellen den Piperidino-, Morpholino-, Thiomorpholino-, Piperazino-, Imidazol-, Theophyllin- oder Pyrrolidinorest dar,
R_4 bedeutet Vinyl oder $CHOHCH_2OH$ und
R_5 bezeichnet Wasserstoff.

4. Pharmazeutische Zusammensetzung nach Anspruch 1, worin die Verbindungen der Gruppe B) aus den durch die Formel III



(III)

charakterisierten Verbindungen, in welcher Formel
R^1, R^4 und R^5, die gleich oder verschieden sein können, für Wasserstoff, Hydroxy, Niederalkoxy, Dialkylphosphinylalkoxy, Acyloxy oder Halogen stehen, zwei der Reste R^1, R^4 oder R^5, wenn sie in benachbarten Positionen vorliegen und zusammengenommen werden, eine Methylendioxy- oder Ethylendioxygruppe bilden können,
R^2 und R^3 die gleich odere verschieden sein können, für Wasserstoff, Hydroxy, Niederalkoxy, Amino, Alkylaminon, Dialkylamino, Arylamino, Amino oder Alkyl, das durch einer 5- oder 6-gliedrigen Kohlenstoffring mit einem Gehalt an bis zu 3 Heteroatomen, ausgewählt aus der Gruppe N, O und S, substituiert ist; Alkyl, Cycloalkyl, Hydroxyalkyl, Alkoxyalkyl, Dialkoxyalkyl, Halogenalkyl, Dialkylaminoalkyl, Aralkyl, Acyl und gegenbenenfalls substituiertes Aryl stehen, wobei Aryl einen aromatischen Kohlenwasserstoffrest mit bis zu 10 Kohlenstoffatomen bezeichnet;
R^2 ein Elektronenpaar angibt, wen R^6 für einen der nachstehend definierten Reste steht, und
R^2 und R^3, zusammen mit den Stickstoffatom, an das sie gebunden sind, einen gegebenenfalls substituierten Stickstoffheterocyclus ausbilden können, der gegebenenfalls ein weiteres Stickstoff- oder Sauerstoffatom enthält, und
R^6 für Wasserstoff, Alkyl, Cycloalkyl, Hydroxyalkyl, Alkoxyxaryl, Dialkoxyalkyl, Halogenalkyl, Dialkylaminoalkyl, Aralkyl, heterocyclisch substituiertes Alkyl, Dialkylphosphinylalkyl, Acyl und gegebenenfalls substituiertes Aryl steht, oder
R^6 ein Elektronenpaar angibt, wenn R^2 einen der vorstehend definierten Reste bezeichnet;
und den Säureadditionssalzen und quaternären Ammoniumverbindungen hievon ausgewählt sind.

5. Pharmazeutische Zusammensetzung nach Anspruch 1, worin die Verbindungen der Gruppe B) aus den folgenden Verbindugen ausgewählt sind:
9,10-Dimethoxy-2-tert.butylamino-6,7-dihydro-4H-pyrimido(6,1-a)isochinolin-4-on-hydrochlorid,
9,10-Dimethoxy-2-(2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido-(6,1-a)isochinolin-4-on-hydrochlorid dihydrat,
9,10-Dimethoxy-3-methyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido-(6,1-a)isochinolin-4-on-hydro chlorid,
9,10-Dimethoxy-2-(N-methyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isochinolin-4-on-hyd rochlorid,

9,10-Dimethoxy-3-isopropryl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isochinolin-4-on-hydrochlorid,
9,10-Dimethoxy-2-(N-isopropyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isochinolin-4-on-hydrochlorid,
9,10-Dimethoxy-3-ethyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido-(6,1-a)isochinolin-4-on-hydrochlorid,
9,10-Dimethoxy-2-(n-ethyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isochinolin-4-on-hydrochlorid,
9,10-Dimethoxy-3-acethyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido-(6,1-a)isochinolin-4-on oder
9,10-Dimethoxy-2-(N-acetyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isochinolin-4-on.

6. Pharmazeutische Zusammensetzung nach Anspruch 1 mit einem Gehalt an 7β-Acetoxy-8,13-epoxy-1α ,6β,9 α-trihydroxy-labd-14-en-11-on und 9,10-Dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido-(6,1-a)isochinolin-4-one-hydrochlorid.

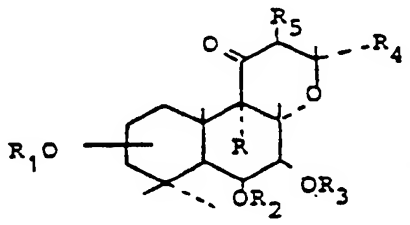
7. Pharmazeutische Zusammensetzung nach einem oder mehreren der Ansprüche 1 bis 6 zur topischen Verabreichung.

8. Verfahren zur Herstellung einer pharmazeutischen Zusammenzetzung nach den Ansprüchen 1 bis 7, worin wenigstens eine Verbindung der Gruppe A) und wenigstens eine Verbindung der Gruppe B) zusammen mit annehmbaren Trägern und/oder Exzipientien in eine zur Verabreichung geeignete Form übergeführt werden.

Patentansprüche für folgende Vertragsstaaten : ES, GR

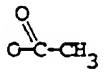
1. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, worin wenigstens eine Verbindung aus einer Gruppe A), bestehend aus Labdanditerpenoidderivaten, und wenigstens eine Verbindung aus einer Gruppe B), bestehend aus Pyrimido(6,1-a)isochinolin-4-one-Derivaten, in eine zur Verabreichtung geeignete Form übergeführt werden.

2. Verfahren nach Anspruch 1, worin die Verbindungen der Gruppe A) aus den durch die Formel I

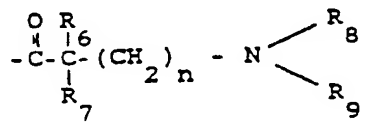


(I)

charakterisierten Verbindungen, in welcher Formel R für H, OH, O-(C_1-C_3)-Alkyl oder



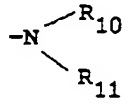
steht, R_1-R_3 unabhängig voneinander Wasserstoff, (C_1-C_6)-Alkyl, (C_1-C_6)-Alkenyl, (C_1-C_6)-Alkinyl, (C_3-C_8)-Cycloalkyl, Dialkylamino oder Aralkyl, worin die Alkylgruppen höschens 4 Kohlenstoffatome aufweisen, (C_1-C_{20})-Acyl, (C_2-C_{10})-Alkoxycarbonyl oder (C_2-C_{10})-Arylaminocarbonyl bedeuten, oder entweder alle drei oder nur zwei oder einer der Substituenten R_1, R_2 und R_3 für einen Rest der Formel II



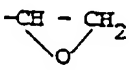
(II)

stehen und der oder die anderen Substituenten Wasserstoff bedeuten, worin R_6 und R_7 gleich oder verschieden sind und Wasserstoff, (C_1-C_6)-Alkyl oder einer Arylrest bedeuten, n für 0 oder eine ganze Zahl von 1 bis 10 steht, R_8 Wasserstoff bezeichnet, wenn R_9 für Wasserstoff, unsubstituiertes oder substituiertes (C_1-C_6)-Alkyl, (C_5-C_7)-Cycloalkyl, Aryl-(C_1-C_2)-alkyl, Aryl, eine heterocyclischen Kohlenwasserstoff, worin die Heteroatome Sauerstoff, Stickstoff oder Schwefel sein können, gegebenenfalls substituiertes Amino, Hydroxyl, Acyl, Di-(C_1-C_6)alkylamino, Carbonyl, (C_1-C_6)-Alkoxycarbonyl, (C_1-C_6)-Alkylcarbonyl-(C_1-C_6)--alkyl steht, oder R_8 und R_9 die gleiche Bedeutung besitzen und für gegenbenfalls substituiertes (C_1-C_6)-Alkyl, Aryl oder Aryl-(C_1-C_2)--alkyl stehen, oder R_8 (C_1-C_6)-Alkyl bezeichnet und R_9 für substituiertes (C_1-C_6)-Alkyl, (C_5-C_7)-Cycloalkyl, Aryl-(C_1-C_6)-alkyl oder Di-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl steht, oder R_8 und R_9 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen heterocyclischen Kohlenwasserstoff bedeuten, der zusätzlich zu dem Stickstoffatom ein oder mehrere Heteroatome aus der Stickstoff, Sauerstoff und Schwefel umfassenden Gruppe enthalten kann und einfach oder mehrfach durch (C_1-C_6)-Alkyl, Aryl-(C_1-C_6)-alkyl, Hydroxy-(C_1-C_6)-alkyl, Aryl, Hydroxyl oder weitere heterocyclische Kohlenwasserstoffe substituiert sein kann, oder R_1, R_2 und/oder R_3 für

stehen, worin Z Sauerstoff oder Schwefel bedeutet und A entweder einen Rest

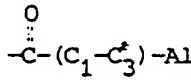


darstellt, worin R_{10} Wasserstoff oder (C_1-C_6)-Alkyl bedeutet und R_{11} (C_1-C_6)-Alkyl, (C_3-C_7)-Cycloalkyl, Aryl, Aryl-(C_1-C_6)-alkyl, (C_2-C_6)-Carbalkoxy oder Sulfonylaryl darstellt, oder R_{10} und R_{11}, gemeinsam mit dem Stickstoffatom, an das sie gebunden sind, einen Heterocyclus ausbilden, der als weiteres Heteroatom Sauerstoff, Stickstoff oder Schwefel enthalten kann, oder A den Rest -OR_{12} bedeutet, worin R_{12} für (C_1-C_6)-Alkyl oder Halogen-(C_1-C_6)-alkyl steht, oder R_1 eine Tris-(C_1-C_6)-alkyl-silylgruppe bedeutet, und R_2 und R_3 die oben angeführten Bedeutungen aufweisen, R_4 für Ethyl, eine Vinylgruppe, -CHO,



oder -CH(OX)CH_2OX steht, worin X Wasserstoff oder -C(O)-(C_1-C_3)-Alkyl ist und R_5 für Wasserstoff, OH oder O-(C_1-C_3)-Alkyl steht, und den pharmazeutisch annehmbaren Salzen hievon ausgewählt sind.

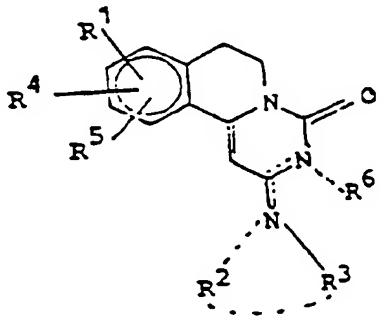
3. Verfahren nach Anspruch 1, worin die Verbindugen der Gruppe A) aus der Gruppe von Verbindungen der Formel I, wie in Anspruch 2 beansprucht, ausgewählt sind, die durch wenigstens eines der folgenden Merkmale charakterisiert sind:
R steht für H oder OH,
R_1-R_3 bedeuten unabhängig voneinander Wasserstoff oder



oder alle drei, zwei oder einer der Substituenten R_1-C_3 bezeichnet die Gruppe der Formel II, wie vorstehend beschrieben, worin n eine ganze Zahl von 0 bis 5 ist und der oder die anderen Substituenten Wasserstoff darstellen,
R_6 und R_7 bedeuten Wasserstoff oder R_6 steht für Wasserstoff und R_7 bedeutet (C_1-C_4)-Alkyl,
R_8 bedeutet (C_1-C_{10})-Alkyl und
R_9 bedeutet Cyclohexyl oder R_8 und R_9, gemeinsam mit dem Stickstoffatom, an das sie gebunden sind,

stellen den Piperidino-, Morpholino-, Thiomorpholino-, Piperazino, Imidazol-, Theophyllin- oder Pyrrolidinorest dar,
R_4 bedeutet Vinyl oder $CHOHCH_2OH$ und
R_5 bezeichnet Wasserstoff.

4. Verfahren nach Anspruch 1, worin die Verbindugen der Gruppe B) aus den durch die Formel III



(III)

charakterisierten Verbindungen, in welcher Formel
R^1, R^4 und R^5, die gleich oder verschieden sein können, für Wasserstoff, Hydroxy, Niederalkoxy, Dialkylphosphinylalkoxy, Acyloxy oder Halogen stehen, zwei der Reste R^1, R^4 oder R^5, wenn sie in benachbarten Positionen vorliegen und zusammengenommen werden, eine Methylendioxy- oder Ethylendioxygruppe bilden können,
R^2 und R^3 die gleich oder verschieden sein können, für Wasserstoff, Hydroxy, Niederalkoxy, Amino, Alkylamino, Dialkylamino, Arylamino, Amino oder Alkyl, das durch einen 5- oder 6-gliedrigen Kohlenstoffring mit einem Gehalt an bis zu 3 Heteroatomen, ausgewählt aus der Gruppe N, O und S, substituiert ist; Alkyl, Cycloalkyl, Hydroxyalkyl, Alkoxyalkyl, Dialkoxyalkyl, Halogenalkyl, Dialkylaminoalkyl, Aralkyl, Acyl und gegebenenfalls substituiertes Aryl stehen, wobei Aryl einen aromatischen Kohlenwasserstoffrest mit bis zu 10 Kohlenstoffatomen bezeichnet;
R^2 ein Elektronenpaar, angibt, wenn R^6 für einen der nachstehend definierten Reste steht, und
R^2 und R^3, zusammen mit dem stickstoffatom, an das sie gebuden sind, einen gegebenenfalls substituierten Stickstoffheterocyclus ausbilden können, der gegebenenfalls ein weiteres Stickstoff- oder Sauerstoffatom enthält, und
R^6 für Wasserstoff, Alkyl, Cycloalkyl, Hydroxyalkyl, Alkoxyxaryl, Dialkoxyalkyl, Halogenalkyl, Dialkylaminoalkyl, Aralkyl, heterocyclisch substituiertes Alkyl, Dialkylphosphinylalkyl, Acyl und gegebenenfalls substituiertes Aryl steht, oder
R^6 ein Elektronenpaar angibt, wenn R^2 einen der vorstehend definierten Reste bezeichnet;
und den Säureadditionssalzen und quaternären Ammoniumverbindungen hievon ausgewählt sind.

5. Verfahren nach Anspruch 1, worin die Verbindungen der Gruppe B) aus den folgenden Verbindungen ausgewählt sind:
9,10-Dimethoxy-2-tert.butylamino-6,7-dihydro-4H-pyrimido(6,1-a)isochinolin-4-on-hydrochlorid,
9,10-Dimethoxy-2-(2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido-(6,1-a)isochinolin-4-on-hydrochlorid-dihydrat,
9,10-Dimethoxy-3-methyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido-(6,1-a)isochinolin-4-on-hydrochlorid,
9,10-Dimethoxy-2-(N-methyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isochinolin-4-on-hydrochlorid,
9,10-Dimethoxy-3-isopropyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isochinolin-4-on-hydrochlorid,
9,10-Dimethoxy-2-(N-isopropyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isochinolin-4-on-hydrochlorid,
9,10-Dimethoxy-3-ethyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido-(6,1-a)isochinolin-4-on-hydrochlorid,
9,10-Dimethoxy-2-(n-ethyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isochinolin-4-on-hyrochlorid,

9,10-Dimethoxy-3-acetyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido-(6,1-a)isochinolin-4-on oder 9,10-Dimethoxy-2-(N-acetyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isochinolin-4-on.

6. Verfahren nach Anspruch 1 mit einem Gehalt an 7β-Acetoxy-8,13-epoxy-1 α,6β,9α-trihydroxy-labd-14-en-11-on und 9,10-Dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido(6,1-a)isochinolin-4-on-hydrochlorid.

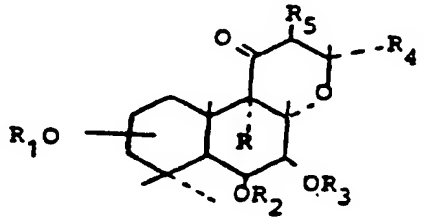
7. Pharmazeutische Zusammensetzung nach einem oder mehreren der Ansprüche 1 bis 6 zur topischen Verabreichung.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL

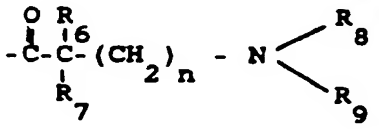
1. Composition pharmaceutique contenant au moins un composé du groupe A) comprenant des dérivés diterpénoïdes de labdane et au moins un composé du groupe B) comprenant des dérivés de la pyrimido(6,1-a)isoquinoléin-4-one.

2. Composition pharmaceutique telle que revendiquée dans la revendication 1, dans laquelle les composés du groupe A) sont choisis parmi les composés caractérisés par la formule I



(I)

dans laquelle R représente H, OH, O-(C_{1-3})-alkyle ou $OCOCH_3$, R_1 à R_3, indépendamment les uns des autres, représentent H, alkyle en C_{1-6}, alkènyle en C_{1-6}, alkynyle en C_{1-6}, cycloalkyle en C_{3-8}, dialkylamino ou aralkyle dans lesquels les groupes alkyle possèdent au plus 4 atomes de carbone, acyle en C_{1-20}, alcoxy(C_{2-10})-carbonyle, aryl(C_{2-10})-aminocarbonyle, ou bien les trois substituants R_1, R_2 et R_3 ou seulement un ou deux des substituants R_1, R_2 et R_3 représente(nt) le radical de formule II



(II)

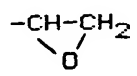
et l'autre ou les autres représentent l'atome d'hydrogène, R_6 et R_7 étant identiques ou différents et représentant H, alkyle en C_{1-6} ou aryle, n vaut 0 ou un nombre entier de 1 à 10, R_8 représente H si R_9 est H, alkyle en C_{1-6} substitué ou non substitué, cycloalkyle en C_{5-7}, arylalkyle(C_{1-2}), aryle, un hydrocarbure hétérocyclique dans lequel les hétéroatomes peuvent être oxygène, azote ou soufre, amino éventuellement substitué, hydroxyle, acyle, dialkyl(C_{1-6})amino, carbonyle, alcoxy(C_{1-6})carbonyle, alkyl(C_{1-6})carbonylalkyl(C_{1-6}), ou R_8 et R_9 ont la même signification et représentent alkyle en C_{1-6} éventuellement substitué, aryle ou arylalkyle(C_{1-2}), ou R_8 représente alkyle en C_{1-6} et R_9 représente alkyle en C_{1-6} substitué, cycloalkyle en C_{5-7}, arylalkyle(C_{1-6}) ou dialkyl(C_{1-6})aminoalkyl(C_{1-6}), ou bien R_8 et R_9, ensemble avec l'atome d'azote auquel ils sont liés, représentent un hydrocarbure hétérocyclique qui peut contenir, en plus de l'atome d'azote, un ou plusieurs héréroatomes pris dans le groupe comprenant l'azote, l'oxygène et le soufre, et qui peut être substitué par un ou plusieurs groupes alkyle en C_{1-6}, arylalkyle(C_{1-6}), hydroxyalkyle(C_{1-6}), aryle, hydroxyle, ou d'autres hydrocarbures hétérocycliques, ou bien R_1, R_2 et/ou R_3 repré-

sente(nt) -C(=Z)A, où Z est O ou S, et A représente soit le radical $-NR_{10}R_{11}$, dans lequel R_{10} est H ou alkyle en C_{1-6} et R_{11} représente alkyle en C_{1-6}, cycloalkyle en C_{3-7}, aryle, arylalkyle(C_{1-6}), alkoxy(C_{2-6})carbonyle ou sulfonylaryle, ou bien R_{10} et R_{11}, ensemble avec l'atome d'azote auquel ils sont liés, forment un hétérocycle qui peut contenir, comme autres hétéroatomes, O, N ou S, ou bien A représente le radical $-OR_{12}$ dans lequel R_{12} représente alkyle en C_{1-6} ou halogénoalkyle en C_{1-6}, ou bien

R_1 représente un groupe tris-alkyl(C_{1-6})silyle, et

R_2 et R_3 ont les définitions données ci-dessus,

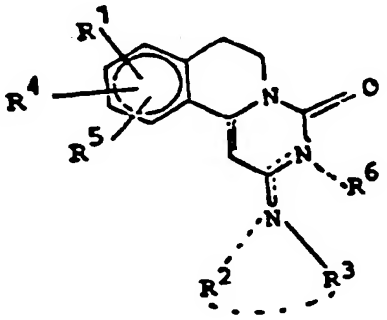
R_4 représente éthyle, vinyle, -CHO,



ou $-CH(OX)CH_2OX$, où X est H ou -C(=O)-alkyle(C_{1-3}) et R_5 représente H, OH ou -O-alkyle(C_{1-3}), ainsi que leurs sels pharmaceutiquement acceptables.

3. Composition pharmaceutique telle que revendiquée dans la revendication 1, dans laquelle les composés du groupe A) sont choisis parmi ceux du groupe de composés de formule I, tels que revendiqués dans la revendication 2, qui sont caractérisés par au moins un des attributs suivants:
R est H ou OH,
R_1 à R_3 représentent, indépendamment l'un de l'autre, H ou -C(=O)-alkyle(C_{1-3}) ou bien un, deux ou trois des substituants
R_1 à R_3 représente(nt) le groupe de formule II, décrit ci-dessus, dans lequel n est un nombre entier valant de 0 à 5, et l'autre ou les autres est (sont) H,
R_6 et R_7 représentent H, ou R_6 représente H et R_7 représente alkyle en C_{1-4},
R_8 représente alkyle en C_{1-10}, et
R_9 représente cyclohexyle, ou bien R_8 et R_9, ensemble avec l'atome d'azote auquel ils sont liés, représentent le radical pipéridino, morpholino, thiomorpholino, pipérazino, imidazolo, théophyllino ou pyrrolidino,
R_4 repésente vinyle ou $CHOHCH_2OH$ et
R_5 représente H.

4. Composition pharmaceutique telle que revendiquée dans la revendication 1, dans laquelle les composés du groupe B) sont choisis parmi les composés caractérisés par la formule III



(III)

dans laquelle
R^1, R^4 et R^5, qui peuvent être identiques ou différents, représentent H, OH, alcoxy inférieur, dialkylphosphinylalcoxy, acyloxy ou halogène, deux des radicaux R^1, R^4 ou R^5, quand ils sont en positions adjacentes et pris ensemble, pouvant former un groupe méthylènedioxy ou éthylènedioxy,
R^2 et R^3, qui peuvent être identiques ou différents, représentent H, OH, alcoxy inférieur, amino, alkylamino, dialkylamino, arylamino, amino ou alkyle substitué par un cycle carbocyclique à 5 ou 6 chaînons contenant jusqu'à 3 hétéroatomes choisis parmi N, O et S, alkyle, cycloalkyle, hydroxyalkyle, alcoxyalkyle, dialcoxyalkyle, halogénoalkyle, diaklylaminoalkyle, aralkyle, acyle et aryle éventuellement substitué, aryle

représentant un radical d'hydrocarbure aromatique comportant jusqu'à 10 atomes de carbone,
R^2 représente une paire d'électrons si R^6 désigne l'un des radicaux définis ci-dessous, et
R^2 et R^3, pris ensemble avec l'atome d'azote auquel ils sont liés, peuvent former un hétérocycle azoté éventuellement substitué pouvant renfermer un autre atome d'azote ou d'oxygène, et
R^6 représente H, alkyle, cycloalkyle, hydroxyalkyle, alcoxyalkyle, dialcoxyalkyle, halogénoalkyle, dialkylaminoalkyle, aralkyle, alkyle substitué par un hétérocycle, dialkylphosphinylalkyle, acyle et aryle éventuellement substitué, ou bien R^6 représente une paire d'électrons si R^2 désigne l'un des radicaux définis ci-dessus,
ainsi que leurs sels d'addition d'acide et sels d'ammonium quaternaire.

5. Composition pharmaceutique telle que revendiquée dans la revendication 1, dans laquelle les composés du groupe B) sont choisis parmi les composés suivants:
chlorhydrate de 9,10-diméthoxy-2-tert-butylamino-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
dihydrate de chlorhydrate de 9,10-diméthoxy-2-(2,4,6-triméthylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-3-méthyl-2-mésitylimino-2,3,6,7-tétrahydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-2-(N-méthyl-2,4,6-triméthylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-3-isopropyl-2-mésitylimino-2,3,6,7-tétrahydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-2-(N-isopropyl-2,4,6-triméthylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-3-éthyl-2-mésitylimino-2,3,6,7-tétrahydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-2-(N-éthyl-2,4,6-triméthylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-3-acétyl-2-mésitylimino-2,3,6,7-tétrahydro-4H-pyrimido(6,1-a)isoquinoléin-4-one, et
chlorhydrate de 9,10-diméthoxy-2-(N-acétyl-2,4,6-triméthylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoléin-4-one.

6. Composition pharmaceutique telle que revendiquée dans la revendication 1, contenant de la 7β-acétoxy-8,13-époxy-1α-6β-9α-trihydroxy-labd-14-èn-11-one et du chlorhydrate de 9,10-diméthoxy-3-éthyl-2-mésitylimino-2,3,6,7-tétrahydro-4H-pyrimido(6,1-a)isoquinoléin-4-one.

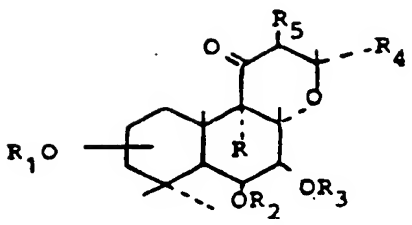
7. Composition pharmaceutique telle que revendiquée dans une ou plusieurs des revendications 1 à 6, pour administration locale.

8. Procédé de préparation d'une composition pharmaceutique, telle que revendiquée dans les revendications 1 à 6 ou 9, dans lequel on transforme au moins un composé du groupe A) et au moins un composé du groupe B), en présence de véhicules et/ou d'excipients acceptables, en une forme convenant à l'administration.

Revendications pour les Etats contractants suivants : ES, GR

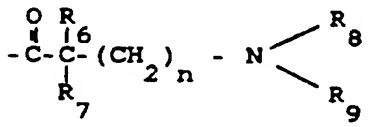
1. Procédé de préparation d'une composition pharmaceutique, dans lequel on transforme en une forme convenant à l'administration au moins un composé du groupe A) comprenant des dérivés diterpénoïdes de labdane et au moins un composé du groupe B) comprenant des dérivés de la pyrimido (6,1-a)isoquinoléin-4-one.

2. Procédé tel que revendiqué dans la revendication 1, dans lequel les composés du groupe A) sont choisis parmi les composés caractérisés par la formule I



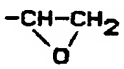
(I)

dans laquelle R représente H, OH, O-(C_{1-3})-alkyle ou $OCOCH_3$, R_1 à R_3, indépendamment les uns des autres, représentent H, alkyle en C_{1-6}, alkényle en C_{1-6}, alkynyle en C_{1-6}, cycloalkyle en C_{3-8}, dialkylamino ou aralkyle dans lesquels les groupes alkyle possèdent au plus 4 atomes de carbone, acyle en C_{1-20}, alcoxy(C_{2-10})-carbonyle, aryl(C_{2-10})-aminocarbonyle, ou bien les trois substituants R_1, R_2 et R_3 ou seulement un ou deux des substituants R_1, R_2 et R_3 représente(nt) le radical de formule II



(II)

et l'autre ou les autres représentent l'atome d'hydrogène, R_6 et R_7 étant identiques ou différents et représentant H, alkyle en C_{1-6} ou aryle, n vaut 0 ou un nombre entier de 1 à 10, R_8 représente H si R_9 est H, alkyle en C_{1-6} substitué ou non substitué, cycloalkyle en C_{5-7}, arylalkyle(C_{1-2}), aryle, un hydrocarbure hétérocyclique dans lequel les hétéroatomes peuvent être oxygène, azote ou soufre, amino éventuellement substitué, hydroxyle, acyle, dialkyl(C_{1-6})amino, carbonyle, alcoxy(C_{1-6})carbonyle, alkyl(C_{1-6})carbonylalkyl(C_{1-6}), ou R_8 et R_9 ont la même signification et représentent alkyle en C_{1-6} éventuellement substitué, aryle ou arylalkyle(C_{1-2}), ou R_8 représente alkyle en C_{1-6} et R_9 représente alkyle en C_{1-6} substitué. Cycloalkyle en C_{5-7}, arylalkyle(C_{1-6}) ou dialkyl(C_{1-6})aminoalkyl(C_{1-6}), ou bien R_8 et R_9, ensemble avec l'atome d'azote auquel ils sont liés, représentent un hydrocarbure hétérocyclique qui peut contenir, en plus de l'atome d'azote, un ou plusieurs hétéroatomes pris dans le groupe comprenant l'azote, l'oxygène et le soufre, et qui peut être substitué par un ou plusieurs groupes alkyle en C_{1-6}, arylalkyle(C_{1-6}), hydroxyalkyle(C_{1-6}), aryle, hydroxyle, ou d'autres hydrocarbures hétérocycliques, ou bien R_1, R_2 et/ou R_3 représente(nt) -C(=Z)A, où Z est O ou S, et A représente soit le radical -$NR_{10}R_{11}$, dans lequel R_{10} est H ou alkyle en C_{1-6} et R_{11} représente alkyle en C_{1-6}, cycloalkyle en C_{3-7}, aryle, arylalkyle(C_{1-6}), alcoxy(C_{2-6})carbonyle ou sulfonylaryle, ou bien R_{10} et R_{11}, ensemble avec l'atome d'azote auquel ils sont liés, forment un hétérocycle qui peut contenir, comme autres hétéroatomes, O, N ou S, ou bien A représente le radical -OR_{12} dans lequel R_{12} représente alkyle en C_{1-6} ou halogénoalkyle en C_{1-6}, ou bien
R_1 représente un groupe tris-alkyl(C_{1-6})silyle, et
R_2 et R_3 ont les définitions données ci-dessus,
R_4 représente éthyle, vinyle, -CHO,

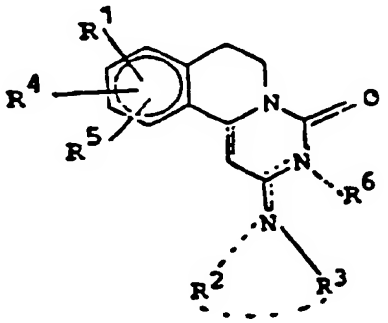


ou -CH(OX)CH_2OX, où X est H ou -C(=O)-alkyle(C_{1-3}) et R_5 représente H, OH ou -O-alkyle(C_{1-3}), ainsi que leurs sels pharmaceutiquement acceptables.

3. Procédé tel que revendiqué dans la revendication 1, dans lequel les composés du groupe A) sont choisis parmi ceux du groupe de composés de formule I, tels que revendiqués dans la revendication 2, qui sont caractérisés par au moins un des attributs suivants:
R est H ou OH,
R_1 à R_3 représentent, indépendamment l'un de l'autre, H ou -C(=O)-alkyle(C_{1-3}) ou bien un, deux ou trois

des substituants R_1 à R_3 représente(nt) le groupe de formule II, décrit ci-dessus, dans lequel n est un nombre entier valant de 0 à 5, et l'autre ou les autres est (sont) H,
R_6 et R_7 représentent H, ou R_6 représente H et R_7 représente alkyle en C_{1-4},
R_8 représente alkyle en C_{1-10}, et
R_9 représente cyclohexyle, ou bien R_8 et R_9, ensemble avec l'atome d'azote auquel ils sont liés, représentent le radical pipéridino, morpholino, thiomorpholino, pipérazino, imidazolo, théophyllino ou pyrrolidino,
R_4 représente vinyle ou $CHOHCH_2OH$ et
R_5 représente H.

4. Procédé tel que revendiqué dans la revendication 1, dans lequel les composés du groupe B) sont choisis parmi les composés caractérisés par la formule III



(III)

dans laquelle
R^1, R^4 et R^5, qui peuvent être identiques ou différents, représentent H, OH, alcoxy inférieur, dialkylphosphinylalcoxy, acyloxy ou halogène, deux des radicaux R^1, R^4 ou R^5, quand ils sont en positions adjacentes et pris ensemble, pouvant former un groupe méthylènedioxy ou éthylènedioxy,
R^2 et R^3, qui peuvent être identiques ou différents, représentent H, OH, alcoxy inférieur, amino, alkylamino, dialkylamino, arylamino, amino ou alkyle substitué par un cycle carbocyclique à 5 ou 6 chaînons contenant jusqu'à 3 hétéroatomes choisis parmi N, O et S, alkyle, cycloalkyle, hydroxyalkyle, alcoxyalkyle, dialcoxyalkyle, halogénoalkyle, dialkylaminoalkyle, aralkyle, acyle et aryle éventuellement substitué, aryle représentant un radical d'hydrocarbure aromatique comportant jusqu'à 10 atomes de carbone,
R^2 représente une paire d'électrons si R^6 désigne l'un des radicaux définis ci-dessous, et R^2 et R^3, pris ensemble avec l'atome d'azote auquel ils sont liés, peuvent former un hétérocycle azoté éventuellement substitué pouvant renfermer un autre atome d'azote ou d'oxygène, et
R^6 représente H, alkyle, cycloalkyle, hydroxyalkyle, alcoxyalkyle, dialcoxyalkyle, halogénoalkyle, dialkylaminoalkyle, aralkyle, alkyle substitué par un hétérocycle, dialkylphosphinylalkyle, acyle et aryle éventuellement substitué, ou bien R^6 représente une paire d'électrons si R^2 désigne l'un des radicaux définis ci-dessus,
ainsi que leurs sels d'addition d'acide et sels d'ammonium quaternaire.

5. Procédé tel que revendiqué dans la revendication 1, dans lequel les composés du groupe B) sont choisis parmi les composés suivants:
chlorhydrate de 9,10-diméthoxy-2-tert-butylamino-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
dihydrate de chlorhydrate de 9,10-diméthoxy-2-(2,4,6-triméthylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-3-méthyl-2-mésitylimino-2,3,6,7-tétrahydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-2-(N-méthyl-2,4,6-triméthylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-3-isopropyl-2-mésitylimino-2,3,6,7-tétrahydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-2-(N-isopropyl-2,4,6-triméthylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,

chlorhydrate de 9,10-diméthoxy-3-éthyl-2-mésitylimino-2,3,6,7-tétrahydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-2-(N-éthyl-2,4,6-triméthylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoléin-4-one,
chlorhydrate de 9,10-diméthoxy-3-acétyl-2-mésitylimino-2,3,6,7-tétrahydro-4H-pyrimido(6,1-a)isoquinoléin-4-one, et
chlorhydrate de 9,10-diméthoxy-2-(N-acétyl-2,4,6-triméthylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinoléin-4-one.

6. Procédé tel que revendiquée dans la revendication 1, utilisant de la 7β-acétoxy-8,13-époxy-1α,6β,9α-trihydroxy-labd-14-èn-11-one et du chlorhydrate de 9,10-diméthoxy-3-éthyl-2-mésitylimino-2,3,6,7-tétrahydro-4H-pyrimido(6,1-a)isoquinoléin-4-one.

7. Composition pharmaceutique telle que revendiquée dans une ou plusieurs des revendications 1 à 6, pour administration locale.